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NDA 28-193

1 OF 7

NDAZO-193

AP Ltr

AE Ltr

N/A Ltr

Major Pharm/

Bio

Pharm./Tox

Stat

Chem

EA/Fonsi

FDA Corres.

Co. Corres

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

AP Ltr

AE Ltr



Food and Drug Administration
Rockville MD 20857

NDA 20-193

Baker Norton Pharmaceuticals, Inc.
4400 Biscayne Boulevard
Miami, Florida 33137

SEP 2 1996

Attention: Ed Mitchell, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Mitchell:

Please refer to your June 11, 1991, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elmiron (pentosan polysulfate sodium) Capsules.

We acknowledge receipt of your correspondence and amendments dated August 28 and 30, September 9, 10, and 11, and October 3 and 28, 1991; January 22 and 27, June 2 and 22, November 9, and December 10, 1992; February 4, March 2, April 6 and 20, May 26, June 2, and July 7 and 20, 1993; February 11, November 8, and December 28, 1994; January 25, March 2, May 22, June 19, August 31, October 26 and 30, and December 1 (2) and 11, 1995; and January 31, February 15, March 4, April 10, May 6, August 12, and September 3, 13 and 20 1996. We also acknowledge receipt of a correspondence (undated) on February 17, 1994.

This new drug application provides for a semi-synthetically produced heparin-like macromolecular carbohydrate derivative indicated for the relief of pain or discomfort associated with interstitial cystitis.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. The labeling includes a Medication Guide for patients. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL, including patient package insert, as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-193. Approval of this submission by FDA is not required before the labeling is used.

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Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated April 10 and September 20, 1996. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

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In addition, please submit three copies of the introductory promotional material, revised in accordance with approved labeling, that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Medical Imaging and Radiopharmaceutical Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Susan L. Cusack
Consumer Safety Officer
(301) 443-3500

Sincerely yours,

Paula Botstein 9/26/96

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:

Labeling dated September 25, 1996.

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cc:

Original NDA 20-193

HFD-160/Div. files

HFD-160/CSO/Cusack

HFD-160/Paserchia/Love/Hunt/Lee/Davi/Welch

HFD-2/M.Lumpkin

HFD-103/P.Botstein

HFD-101/L.Carter (with labeling)

HFD-820/Yuan Yuan Chiu

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HF-35/Orphan Drugs (with labeling)

HFD-80 (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613 (with labeling)

HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.

drafted: slc/September 19, 1996/20193ap.001

revised: IC/9.25.96/20193ap.002

final:IC/9.25.96

APPROVAL [with Phase 4 Commitments]

Handwritten notes:
K 9/25/96
MJC 9/25/96

MAR 1 1996

NDA 20-193

Baker Norton Pharmaceuticals, Inc.
8800 N.W. 36th Street
Miami, Florida 33178

Attention: Ed Mitchell, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Mitchell:

Please refer to your June 11, 1991, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELMIRON® (pentosan polysulfate sodium) 100 mg capsules.

We acknowledge receipt of your correspondence and amendments dated August 28 and 30, September 9, 10, and 11, and October 3 and 28, 1991; January 22 and 27, June 2 and 22, November 9, and December 10, 1992; February 4, March 2, April 6 and 20, May 26, June 2, and July 7 and 20, 1993; February 11, November 8, and December 28, 1994; January 25, March 2, May 22, June 19, August 31, October 26 and 30, and December 1 (2) and 11, 1995; and January 31, and February 15, 1996. We also acknowledge receipt of a correspondence (undated) on February 17, 1994. Additionally we refer to our not approvable letters dated January 27, 1993, and October 28, 1994.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit revised draft labeling for the drug and provide the following information. The labeling should be identical in content to the enclosed marked-up draft labeling.

Clinical/Statistical

1. Please submit a tabular summary of laboratory data and vital signs derived from the open label physician's usage study (referenced in your submission as a compassionate use study). This should include means, standard deviation, and ranges. Also provide laboratory test normal ranges and highlight any abnormal test results.

Also, please submit contingency tables for clinically relevant pairs (e.g., hematocrit and hemoglobin; platelets and bleeding time or other obtained measures of coagulation; bilirubin and alkaline phosphatase; BUN and creatine).

2. Please perform a demographic subset analysis for safety (age, race, gender) for the pivotal and open label physician's usage study databases.
3. Please submit the case report forms (CRF) for the remaining 26 patients with serious adverse events as reported in appendix F in the June, 1995, Investigators Brochure. Also, please provide CRFs for patients reporting alopecia. Include line listings and an analysis of these events (i.e., number of patients, time of occurrence, extent, location previous history, resolution, treatment, concomitant medications). Include your evaluation and assessment of alopecia induced by chemically similar drugs, with copies and evaluation of relevant published literature.
4. Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding pentosan polysulfate sodium. Please provide updated information as listed below:
 - a. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the current NDA amendment was submitted and any subsequent reactions will facilitate the review.
 - b. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.
 - c. Provide details of any significant changes or findings, if any.
 - d. Summarize worldwide experience on the safety of this drug. Submit copies of labeling, with translation to English if needed, from any country in which the drug is marketed.
 - e. Please submit case report forms for any patients studied since the submission of the August 31, 1995, amendment, who died during treatment or withdrew from the study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

5. Please devise a Patient Package Insert which we will review in conjunction with your response to the Pharmacokinetic and Clinical sections of this letter. Enclosed is a format guide to follow when developing this insert.
6. Please provide the structural formula of the active ingredient of Hemoclar and say whether you think it is chemically identical to that of Elmiron.

Biopharmaceutics/Pharmacokinetics

Previous non-approval letters requested data to validate the assay used in the pharmacokinetic studies and the requested raw data from these studies. In order to complete the package insert, please provide the data requested in the attached draft labeling dated February 29, 1996. These data should be provided as raw data tables including means and ranges as well as assay validation information.

Labeling

Please submit revised draft labeling which is identical to the attached marked up draft dated February 29, 1996. Notable changes include: new headings and subheadings in the CLINICAL PHARMACOLOGY section, a new CLINICAL TRIALS section, and revisions in the PRECAUTIONS, OVERDOSE, ADVERSE EVENTS, DOSAGE AND ADMINISTRATION sections.

Phase 4

Please commit to undertake and report on the following phase 4 studies:

Protocols for these studies should be submitted within 6 months of the final NDA approval. Actual studies should be initiated within 6 months of final agreement on protocol design. If additional information relating to the safety and effectiveness of the drug become available, further revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Medical Imaging and Radiopharmaceutical Drug Products and two copies of both the promotional material and the package insert directly to:

**Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857**

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Susan Cusack
Consumer Safety Officer
(301) 443-1560

Sincerely yours,

Paula Botstein MD 3/1/96

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

- Enclosures:
1. Draft package insert dated February 29, 1996
 2. Patient Package Insert format guide.

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cc:

Original NDA 20-193

HFD-160/Div. files

HFD-160/CSO/Cusack

HFD-160/

HFD-2/M.Lumpkin

HFD-100

DISTRICT OFFICE

HFD-80 (with draft labeling)

HFD-240/S.Sherman (with draft labeling)

HFD-638 (with draft labeling)

drafted: slc/February 22, 1996/n20193ae.002

R/D init by: DBailey, RDavi, ELeutzinger-02-14-96/NSmith, DLee-02-15-96/
LPaserchia-02-22-96

revised:Cheever/2.22.96/ N:\LOVE\N20193AE.003

revised:Cusack/2.23.96/N:\LOVE\N20193AE.004

revised:Cusack/2.23.96/N:\LOVE\N20193AE.005

revised:Botstein/2.26.96

revised:Cheever/2.27.96/ N:\LOVE\ELMIRON\N20193AE.006

revised:Love/2.28.96/N:\LOVE\ELMIRON\N20193AE.007

revision init by: RDavi, L Paserchia, J Cheever, P Love/2.28.96

revised:Botstein/2.28.96

revised:Cusack/2.29.96/N:\LOVE\ELMIRC\N20193AE.008

F/T:O'Connor/2-29-96

APPROVABLE (AE)

M. Paserchia
2/29/96

Stat/mor

A Statistical and Medical Review of an Amendment

to the New Drug Application

for Elmiron® (Pentosan Polysulfate)

NDA# 20193

Authors:

Ruthanna C. Davi, MS (Statistical Reviewer)

Lori A. Paserchia, MD (Medical Reviewer)

SPONSOR:	Baker Norton Pharmaceuticals, Inc.
DOC. DATE:	August 31, 1995
REVIEWERS RECEIVED:	September 25, 1995
REVIEWED:	December 13, 1995
REVISIONS:	December 18, 1995
	January 29, 1996
	February 22, 1996
FINAL:	January 31, 1996

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INTRODUCTION

Elmiron is a polysaccharide-based drug that is sponsored by Baker Norton Pharmaceuticals to treat patients with a diagnosis of interstitial cystitis. The proposed indication is for the relief of pain uniquely associated with interstitial cystitis. The proposed dosage is 100 mg by mouth 3 times daily.

Elmiron was designated as an orphan drug product in 1985. The NDA has received 2 nonapproval letters since its original submission in 1991, and hence has been amended on numerous occasions.

This combined statistical and medical review provides a thorough, but brief, summary of the pertinent issues and events that occurred through August 30, 1995. This review then proceeds with a focused critique of the August 31, 1995 amendment to this NDA.

BACKGROUND

1.1 *Scientific: Current Status of Interstitial Cystitis*

- Interstitial cystitis (IC) is a multifactorial syndrome with a natural history that varies from patient to patient.
- Despite years of clinical research, the etiology of IC is still undetermined. A number of theories have been proposed including: bladder ischemia, allergy/autoimmune process, infection and a defective bladder glycosaminoglycan layer leading to unobstructed entry into the bladder wall of irritants naturally found in the urine.¹
- The typical symptomatology of a patient suffering from IC is one of bladder/pelvic pain with marked urinary frequency, urgency and nocturia. These symptoms characteristically occur in a crescendo/decrescendo pattern that is not predictable. Complications include sleep deprivation (due to the continual nocturia), and emotional distress. Patients typically see 5 physicians before a diagnosis of IC is considered. In general, a poor quality of life is characteristic for a patient with IC.
- Without knowledge of the pathophysiology, efficient and effective treatment and research of IC are difficult.
- Criteria established by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) are used to diagnose patients for clinical and research purposes. The inclusion criteria are:
 - bladder pain or urgency
 - glomerulations or Hunner's ulcers noted upon cystoscopy
 - ≥ 8 voids/day
 - ≥ 1 episode of nocturia/night
 - awake bladder capacity ≤ 350 ml on medium-fill CMG
 - intense urge to void a ≤ 150 ml on medium-fill CMG¹

The exclusion criteria are:

- detrusor instability
 - symptom duration < 9 months
 - symptoms relieved by antibiotics, antispasmodics, urinary tract analgesics
 - known causes for symptoms (radiation cystitis, ureteral stone, vaginitis, urinary tract infection).¹
- Numerous treatment modalities have been instituted with variable, and usually temporary, success. Diet modification, behavior modification, and treatment to overcome sleep deprivation provide improvement in symptomatology in about 40% of patients.² Intravesicular administration of heparin, lidocaine, antibiotics,

sodium bicarbonate solution, and steroids (singularly and as "cocktails") have been tried.¹ Intravesicular administration of dimethyl sulfoxide (DMSO), the only FDA-approved treatment for IC, has also been used.

- At the present time a marker of the disease and/or of treatment success is not available. The lack of a marker has increased the difficulty of conducting clinical research.

1.2 *Regulatory: Summary to Date*

August 7, 1985

- Elmiron was granted an Orphan Drug designation.

June 11, 1991

- Original NDA submitted (please see the medical officer review dated December 13, 1991 and the Statistical review dated November 8, 1991).

January 27, 1993

- After numerous amendments and correspondence, a nonapproval letter was sent to the sponsor. The nonapproval decision centered around:

Clinical/Statistical

- The submitted NDA lacked the 2 adequate and well-controlled studies needed to determine the effects of the drug as defined in 21 CFR 314.126. Specifically:
 - (1) The sponsor was informed to conduct a "per protocol" analysis and an "intent-to-treat" analysis for each of the 6 efficacy endpoints. If the results of the 2 analyses were different, the sponsor was asked to provide an explanation.
 - (2) Appropriate subgroup analysis should be performed if the study results suggest that the drug may not be equally effective in all patients with interstitial cystitis.
 - (3) The sponsor was asked to reassess the level needed to achieve statistical significance to account for the performance of an interim analysis.
 - (4) The sponsor was asked to justify the statement that adequate relief of symptoms may not be experienced for 6 to 8 weeks after initiating therapy. In other words, the data did not adequately explain the time course of the presumed treatment effect (the change in symptomatology may actually have

been caused by the natural history of the disease and/or by a placebo effect).

- (5) The sponsor was informed that there is a significant investigator interaction. Each study's database was driven by a single, but different, investigator.

N.B.- Safety issues were not a major concern in the original NDA submission (please see the Safety Review section of this review for more details).

Biopharmaceutical

- The information submitted in the NDA did not adequately describe the bioavailability/pharmacokinetic profile of the drug (i.e. compliance with 21 CFR 312.21) and, therefore, did not support approval or the proposed labeling.

Please see Section 2 of this review for more details.

Ultimate Recommendations to the Sponsor

- An additional well-controlled study, ideally utilizing a blinded, randomized withdrawal design, should be performed with 3 of the pivotal study investigators excluded from participating in this study.
- The sponsor should contact the FDA's Division of Biopharmaceuticals to discuss further requirements and study designs.

June 7, 1993

- The sponsor responded to the nonapproval letter by amending the NDA.
- The sponsor incorporated the suggestions made in the nonapproval letter (except for performing an additional study) and re-analyzed the data from the 2 pivotal studies labeled 001 and 002 (please see the Statistical review dated Sept 30, 1993 for an excellent critique of this re-analysis, and of the efficacy database).

October 28, 1994

- A second nonapproval letter was sent to the sponsor.
- Clinical/Statistical nonapproval issues:

- (1) The 2 pivotal studies could not be considered to be independent because the majority of the efficacy database for each study was generated by the same 3 investigators. Upon deletion of the patient results obtained from 1 of these 3 investigators, neither study had the power to show statistical significance for any of the 6 primary efficacy endpoints.

- (2) Upon statistical accounting for multiple comparisons, only 1 of the 6 primary efficacy endpoints achieved statistical significance in study 001 (specifically, decrease in bladder pain based on the change in rating scale from baseline to endpoint). Similarly, only 2 of the 6 primary efficacy endpoints achieved statistical significance in study 002 (specifically, overall improvement based on investigator evaluation [global], and improvement in bladder pain based on patient overall assessment [global]).
- (3) Final FDA conclusion: Study 002 was found to provide some evidence of efficacy (for pain relief); study 001 was deemed unable to support an efficacy claim.

Ultimate Recommendations to the Sponsor

- *Once again, the sponsor was encouraged to conduct another well-controlled study with incorporation of the following suggestions into the protocol:*
 - (1) *increase the sample size to ensure adequate power (given the high drop-out rate noted in the pivotal studies)*
 - (2) *improve the 6-point scale used to assess efficacy; it is not clear how a 4-point questionnaire in the case report form was used to generate this 6-point scale*
 - (3) *either ensure a more homogeneous study population, or more effectively randomize a less homogeneous population upon variables that could affect outcome such as severity of urinary urgency*
 - (4) *prospectively select 1 or 2 objective efficacy endpoints and avoid redundancy*
 - (5) *devise a statistical plan to adjust for multiple comparisons if 1 efficacy endpoint out of multiple endpoints can be used to support efficacy*
 - (6) *exclude any investigators who were involved in study 002*

February 16, 1995

- A meeting with the sponsor was held; the highlights as recorded in the FDA's meeting minutes:
 - (1) the sponsor stated that another study will not be conducted
 - (2) instead the sponsor proposed to conduct an efficacy analysis of the database from the compassionate use study and use this result for the second "pivotal" study

- (3) the FDA expressed uncertainty that this database could be used to support an efficacy claim (at the very least a different type of statistical analysis would be necessary in order for the uncontrolled compassionate use database to qualify as a second study for efficacy) but the FDA stated that it would be considered
- (4) the Division of Biometrics offered to help design a prospective statistical analysis protocol to retrospectively analyze the compassionate use data for efficacy
- (5) the sponsor indicated that not all patients respond to Elmiron, however, previous subset analyses to determine responders versus nonresponders have been unsuccessful
- (6) the sponsor indicated that they were willing to accept a limited indication, and to commit to Phase 4 studies if the product is approved

April 7, 1995

- Recommendations from the Division of Biometrics for a statistical analysis protocol were sent to the sponsor.

August 31, 1995

- Results of the sponsor's analysis of the compassionate use database were submitted to the Division of Biometrics (please see Section 4.0 below for the Statistical review).
- This amendment to the NDA also contained additional information as requested in the second nonapproval letter.
- UNLESS NOTED OTHERWISE, THE FOLLOWING COMBINED BIOMETRICS AND MEDICAL REVIEW IS BASED ON THE INFORMATION SUBMITTED IN THIS AMENDMENT PLUS A NUMBER OF REQUESTS TO THE SPONSOR FOR MORE INFORMATION (AMENDMENTS DATED DECEMBER 1, 1995 AND DECEMBER 11, 1995).

0 PHARMACOKINETIC/PHARMACODYNAMIC REVIEW

- This medical reviewer believes the biopharmaceutical issues should be emphasized at this time, therefore a general profile of the drug is given, a summary of the original Biopharmaceutical review from 1991 is provided, the newest pharmacokinetic (PK) studies are reviewed (by this medical reviewer), the pharmacodynamic (PD) profile is presented, and then a discussion of the major issues follows.

2.1 *General Profile*

- The "active ingredient" in Elmiron is pentosan polysulfate (PPS). PPS is a sulfated polysaccharide comprised of molecules of D-xylose and 4-O-methyl-D-glucuronic acid linked in a 9 to 1 ratio. Hence, PPS is a macromolecule with a molecular weight range of 4000 to 6000 daltons.
- The proposed dosage regimen for Elmiron is 100 mg by mouth 3 times a day.
- To-be-marketed formulation:

100 mg FPS
123 mg microcrystalline cellulose
2 mg magnesium stearate

(capsule)

2.2 *Summary of the Original Biopharmaceutical Review*

N.B. The status of the biopharmaceutical workup has not changed appreciably since 1991. The major concerns:

- (1) the sponsor submitted a total of 6 PK studies; 3 of these studies were journal articles which contained useful information but the validity of the data could not be confirmed
- (2) the other 3 studies were reviewable and had the following flaws:
 - the to-be-marketed capsule formulation was not studied (this was also the case in pivotal study 001)
 - information regarding the validation of the assay for PPS was not provided
 - an inadequate total number of subjects was studied
 - the kinetics of PPS with relation to food ingestion were not characterized
 - the dissolution profiles were inadequate because they were based on a mean of 2 capsules from each of 2 clinical lots
 - a study of the PK of PPS in patients with liver disease was not submitted; this

was an important point because PPS is most likely metabolized by the liver

- the Biopharmaceutical reviewer noted that the results of the best PK study demonstrated that only 11% of the total radioactivity was excreted in the urine after administration of 150 mg TID for 7 days followed by a single dose of 150 mg ³H-PPS; according to the reviewer this corresponded to a mean of 3% of unchanged PPS excreted in the urine

2.3 Pharmacokinetic Profile

- In the August 31, 1995 amendment the sponsor submitted a brief assessment of 7 studies performed by different investigators from 1983 to 1993 (Table 1). Five of these studies were previously submitted with the original NDA in 1991 and are addressed above; the remaining 2 studies are new to the NDA and will be critiqued by this medical reviewer (a formal review by the Division of Biopharmaceutics is pending).

Table 1: A Summary of the Clinical Pharmacokinetics Studies
(reproduced from the August 31, 1995 amendment)

(proposed dose 100 mg TID or ~5 mg/kg/day)

Investigator	Design	Year	Dose/Route	Sample size	Gender
Kummer	open; 2-way crossover	1983	75 mg IV 150 mg po	8	healthy males
Greenslade	open	1983	2, 5, 10 mg/kg po	3	healthy males
McGregor	open	1984	0.1, 1, 7 mg/kg IV; 50 mg/kg IV/SQ	5	healthy males
Forestier	open	1986	50 mg IV	8	pregnant females
Fellstrom	open	1987	40 mg IV 400 mg po	8	healthy males
Losonczy *	open	1991	250-1500 mg po	6	patients with thrombo-embolic disease
Jallad *	double-blind; placebo; randomized; parallel	1993	100, 200, 300, 400 mg po TID	32 (4 groups of 8-- 6 PPS/2 placebo)	healthy males

Legend: * a new study submitted to support the NDA; not reviewed by the Division of Biopharmaceutics in 1991

2.3.1 Review of the Jallad Study

Design

- Goals: determine the safety, PK and PD
- Design: double-blind, placebo-controlled
- Dose: 100, 200, 300 or 400 mg po TID for 6 days (sponsor's proposed dose is 100 mg po TID)
- Sample size: 32 healthy males (6 Elmiron/2 placebo at each dose level)
- PK workup was performed after a single dose and repeated after 6 days of administration. Specific details regarding the PK workup were not submitted.
- The sponsor claims that "unchanged Elmiron was assayed by a radioimmunoassay with a lower limit of detection of about 4 ng/ml." However, detailed information regarding the assay such as how the radioactivity was applied to, or where the radioactive element was placed onto, the Elmiron molecule was not submitted by the sponsor. The validation of the assay was also not discussed.

Results

- Only descriptive statistics were submitted therefore it is not possible to determine the validity of the author's conclusions.
- the PK results:
 - C_{max} ranged from 13 - 54 ng/ml, and plasma AUC ranged from 122 - 1178 ng.hr/ml over the 100 to 400 mg TID dose range (presumably after the first dose)
 - "With repeated administration, the C_{max} and AUC values were higher than after the first dose..."
- the PD was assessed by measuring serum fibrinogen levels:
 - a "moderate decrease" in serum fibrinogen level was observed across the treatment groups; the significance of this finding is unknown since it was generally not accompanied by a change in PT/PTT or bleeding time (only 1 subject had a slight increase in aPTT; please see the safety results below). Unfortunately, a plasma Elmiron concentration v. fibrinogen level curve was not submitted.

- **safety results:**
 - the only ADR's reported were mild nausea and headache in 1 subject who was receiving placebo
 - only 1 subject (in the 400 mg TID Elmiron group) was noted to have an elevation in the PT and aPTT of 1.1 and 2.1x above normal limits, respectively, after 8 days of dosing; the labs returned to within normal limits 6 days after drug discontinuation; the bleeding time was not altered
 - 1 subject in each of the 300 mg TID and 400 mg TID arms, and 2 subjects in the placebo arm had approximately 2-fold elevations in ALT; it is uncertain if the Elmiron was stopped, or if the ALT returned to normal

Reviewer's Conclusion of this Study

- This study, as submitted, provides more useful information regarding the safety than the PK/PD; a more detailed report will be requested in the action letter (this reviewer believes that the product's PK/PD is important but a decision regarding the NDA is not contingent upon this biopharmaceutical information).

2.4 *Pharmacodynamic Profile*

- No information regarding the PD of Elmiron and the urinary bladder has been submitted. This reviewer performed a Medline search which was fruitless.
- In Europe, PPS is administered subcutaneously to produce anticoagulation by decreasing the concentration of activated coagulation factor X, and by inhibiting thrombin generation (however PPS has only 1/15th the ability of heparin to inhibit thrombin generation). Therefore, PPS behaves like a low molecular weight heparin. It must be emphasized, however, that when administered subcutaneously PPS remains "intact". i.e. it is not metabolized as quickly as when given orally. Hence, a greater plasma "intact" PPS concentration is produced. It is presumed that the "intact" molecule is needed for anticoagulation. The similarity of PPS to LMW heparin is discussed further in Section 3.2.

2.4.1 *Review of the Losonczy Study³*

- Goals: determine the PD effect (fibrinolysis, and PT/PTT/thrombin time [TT]) of a stepwise increase in PPS dose

Design

- unblinded, each subject served as his own control

- each of 7 patients had a diagnosis of deep vein thrombosis (DVT) at least 1 year prior to the study (2 patients also had a pulmonary embolism)
- all patients were drug-free for 2 weeks prior to starting the study
- final analysis based on 5 patients because 2 patients dropped out due to recurrence of DVT
- Dose: 250, 500, 750, 1000, 1250, and 1500 mg po (*proposed NDA dose is 100 mg po TID*) were given to each patient on a different day of the week; this reviewer believes that only a single dose was administered for each dose level but it is difficult to determine with certainty from the journal article
- PD workup:

<u>Baseline</u>	<u>2 hr after dose</u>	<u>4 hr after dose</u>
ELT*	ELT*	aPTT/PT/TT
tPA and PAI activity*	tPA and PAI activity*	
aPTT/PT/TT	aPTT/PT/TT	
AST/ALT		

Legend:

- ELT- euglobulin lysis test
- * - checked before and after 10 minutes of venous occlusion
- tPA- tissue plasminogen activator
- PAI- plasminogen activator inhibitor
- aPTT- activated plasma thromboplastin time
- PT- prothrombin time
- TT- thrombin time
- AST- aspartate transaminase
- ALT- alanine transaminase

Results/ Reviewer's Conclusions of this Study

- This entire journal article was poorly written; the methodology and results were especially poorly reported; only descriptive statistics were reported (primarily in graphic form). For this reason, this study does not contribute much useful information.
- Statistically significant prolongation of the TT appears to begin with the lowest dose, 250 mg, but statistically significant prolongation of the PTT doesn't appear to occur until the 750 mg dose level. The PT doesn't change significantly at any dose.
- Statistically significant stimulation of profibrinolytic activity appears to occur at the 250 mg dose level and continues up to the 750 mg dose level.
- This study appears to confirm that hepatic transaminase elevation and diarrhea can be associated with PPS use.

- It is difficult to make a definitive conclusion about the occurrence of thrombocytopenia since the authors' simply stated "The platelet count did not show a *significant* decrease." (Italics added by this reviewer).
- Limitations of the study with regards to the Elmiron NDA:
 - only single doses for each dose level were studied
 - the 100 mg oral dose was not studied
 - a pharmacokinetic analysis was not performed; dose/concentration v. response curves were not generated
 - the authors' did not discuss the possible limitations of their study

2.5 *Medical Reviewer's Conclusions Regarding the Pharmacokinetics and Pharmacodynamics*

- This NDA provides little useful information regarding the PK and PD of Elmiron in the treatment of patients with IC. The only certainty is the poor oral bioavailability of PPS.
- I concur with the conclusions of the Biopharmaceutical reviewer as stated in 1991 that the apparent poor bioavailability is not surprising since this product is very similar, chemically, to a low molecular weight heparin (LMW heparin). In this country (as well as globally), all LMW heparin formulations are administered either subcutaneously or sublingually because the molecule is too large (the MW ranges from daltons) to cross the intestinal endothelium intact. Enzymes found in the endothelium and in the pancreatic secretions would digest the molecule. In addition, if an intact molecule of PPS was to reach the portal circulation, the enzymes in the liver would most certainly metabolize it into smaller fragments and utilize the 5-carbon rings. Therefore, the likelihood of the parent molecule, PPS, reaching the urinary bladder intact (the site of action) is remote.

However, from a regulatory perspective, it is unwise to assume that intact PPS is needed to efficiently and effectively treat patients with IC given the lack a knowledge about IC. Therefore, it is the opinion of this reviewer that the ambiguity surrounding the PK/PD of Elmiron is not sufficient in itself to prevent the approval of the NDA.

- The uncertainty surrounding the assay(s) used in these studies also needs to be addressed. Based on the information submitted by the sponsor, it is difficult to determine if the radioactive assay is measuring intact PPS or fragments of PPS in the urine.
- The uncertainty surrounding the urinary PD of Elmiron is in part due to the lack of information submitted to the NDA, but is also due to the unknown nature of

IC. It is more difficult to study the effects of a drug when the pathophysiology of the disease is unknown.

- The hematologic PD of Elmiron is most likely irrelevant in the IC population because of the dose and route of administration used in this patient population. The relatively small dose and the poor oral bioavailability decrease the chances of achieving a significant plasma concentration of intact PPS. Given the knowledge accumulated with LMW heparins, the intact molecule is probably necessary for producing significant decreases in activated factor X. The same theory applies to the occurrence of heparin-induced thrombocytopenia that is associated with the use of LMW heparin but has not been demonstrated to any significant degree in this NDA (please see Section 3.4.4 of the Safety Review).
- The PK/PD of Elmiron can be further established during Phase 4 should this NDA be approved.

) SAFETY REVIEW

3.1 *Introduction*

- **The safety/toxicity of this product has not been a major concern. In the past 4 years since the NDA was originally filed, the main issues to be solved have centered around efficacy. This point may help to explain why the August, 1995 amendment contained little information regarding the safety of Elmiron. For example, an updated safety database was not submitted for the 2500+ patients in the Compassionate Use study. Of particular importance, an updated database was not submitted for the 200+ patients who dropped out due to an adverse event. The sponsor was reminded that the second nonapproval letter clearly requested that an updated and complete safety database be submitted with any new major amendment. An official FDA request for the sponsor to submit the necessary information (and pertinent case report forms) has been placed; this information has yet to arrive at the FDA.**
- **Given the similarity of Elmiron to low molecular weight (LMW) heparin as noted above, the safety review initially focused on the 2 most frequent and major complications of LMW heparin: thrombocytopenia and hemorrhage.**
- **This section will start with a discussion of the hematologic safety profile of drugs chemically-related to Elmiron. A brief review of the safety data from the original pivotal studies of 1991 will then be presented followed by a critique of the Compassionate Use database.**
- **In Appendix C please see Table 1 for an overall summary of the patient enrollment and discontinuation, and Table 2 for the overall number of ADR's which occurred.**

3.2 *Safety History of Chemically-related Drugs*

3.2.1 *Hemoclar and Other Low Molecular Weight Heparins*

3.2.1.1 *Thrombocytopenia*

- **Hemoclar is a brand of PPS that was manufactured in France by**
- **Dose and indication: 300 mg sublingually daily to treat hyperlipoproteinemias, or 100 mg daily by intramuscular or subcutaneous injection to produce anticoagulation.**
- **Hemoclar was used exclusively in France from 1961 to 1994 before it was removed from the market by French officials due to an unacceptable risk/benefit**

ratio.

- From 1978 to 1986, 53 reports were noted of delayed immunoallergic thrombocytopenia occasionally associated with hemorrhage or thrombosis. Fifty-one of the 53 reports occurred with the use of the parenteral formulation. Hence, the Sanofi formulation of PPS produced the same type of thrombocytopenic complication that has been associated with either fractionated (i.e. LMW) or unfractionated heparin use. The syndrome is referred to as heparin-induced thrombocytopenia (HITP).
- In patients with mild HITP, platelet counts typically decrease to $< 100,000/\text{mm}^3$ but $> 50,000/\text{mm}^3$ within a week of initiating therapy and the patient is asymptomatic; however, in a more severe case the count can drop to $< 50,000/\text{mm}^3$ by the second week of therapy and be associated with either hemorrhage or thrombosis. The platelet count returns to normal within a week of discontinuing the drug.
- The currently touted mechanism for severe HITP is the formation of platelet factor 4/drug complexes which trigger an autoimmune response.
- HITP incidence:

unfractionated heparin =	10% (1% severe)
LMW heparin =	$< < 10\%$
	(various formulations/manufacturers but the dose is comparable)
- The sponsor stated that an "exhaustive international literature search prior to and subsequent to the Sanofi withdrawal did not uncover other reports of significant pentosan polysulfate-related thrombocytopenia outside of France."

3.2.1.2 Hemorrhage

- As expected, both unfractionated heparin and LMW heparin are associated with minor and major bleeding complications. The literature is somewhat unclear which, if either, type of heparin is associated with more bleeding complications. The Hemoclar reports from France that were submitted by the sponsor do not note any bleeding complications except when associated with severe HITP.

3.2.1.3 Laboratory Test Abnormalities

- Both unfractionated heparin and LMW heparin can be associated with elevation of the liver transaminases which typically return to baseline after discontinuation of the drug. The French package insert for Hemoclar that was submitted by the sponsor notes transaminase elevation as an adverse reaction.

Impression

- Hemoclar is distinct from Elmiron: a different manufacturer, a different formulation, and a different route of administration. This reviewer believes that the different route of administration, orally instead of parenterally, is the most significant reason to doubt that Elmiron will demonstrate the same thrombocytopenic complication as Hemoclar and other LMW heparins. The limited pharmacokinetic profile simply does not hint that the bioavailability of intact PPS is sufficient to significantly complex with platelet factor 4. This impression is supported by the results of the pivotal and Compassionate Use studies that are discussed below.

3.3 *Pivotal Studies*

3.3.1 *Introduction*

- There were 2 pivotal studies: 001 and 002.

Study design

- double-blind, randomized and placebo-controlled
- dose: 100 mg orally 3 times daily for 3 months
- only study 002 used the to-be-marketed capsule formulation-- the difference was in the cellulose content: 80 mg for study 001 v. 123 mg for study 002 (the PPS was identical in both studies); the different capsule formulation will have the largest impact on the dissolution kinetics; from the point of view of the safety, this reviewer believes that the difference in capsule formulation does not preclude the evaluation and use of safety data from study 001
- inclusion/exclusion criteria were comparable between the 2 studies and designed to enter patients with moderate to severe symptomatology
- safety monitoring: a physical examination, an adverse drug reaction (ADR) assessment (where the investigator asks the patient if any ADR's have occurred) and an appropriate battery of laboratory tests were checked at baseline and at 3 months

- drop-outs:

Study 001

110 patients entered
(54 Elmiron/56 placebo)

12 drop outs

3 due to ADR

9 non-ADR

2 placebo (1- diarrhea; 1- joint pain)
1 Elmiron (headache, nausea, severe mood swings, suicidal ideation)

Study 002

148 patients entered
(74 Elmiron/74 placebo)

18 drop outs

8 due to ADR

10 non-ADR

5 placebo

1- nausea, diarrhea, runny eyes
1- increased pain
1- attempted suicide
1- side to side eye movements
1- nausea, vomiting, diarrhea, headache, jaundice
1- bowel obstruction*
1- yeast infection, increased nocturia
1- watery eyes, increased mole size, rhinorrhea

3 Elmiron

* deemed by the medical reviewer in 1991 as unrelated to Elmiron

3.3.2 Death and Serious Adverse Drug Reaction Reports

- There were no deaths or serious ADR's reported for the pivotal studies.

3.3.3 General Reports of Adverse Drug Reactions

- Below is a portion of a table from the 1991 medical review. The ADR's presented in Table 2 were chosen as a comparison for the Compassionate Use study ADR database that follows in Tables 5 and 7 of this review.

Table 2: Number and Percentage of Subjects who Experienced Each Adverse Drug Reaction (ADR) in the Original Pivotal Studies (per study, and integrated) (Adapted from the 1991 medical review; selected ADR's correspond with the most common ADR's noted in the Compassionate Use study)

ADR	Study 001 (n = 110)		Study 002 (n = 148)		Integrated (n = 258)	
	Elmiron	Placebo	Elmiron	Placebo	Elmiron	Placebo
nausea	2 (3.8%)	0	1 (1.4%)	3 (4.1%)	3	3
diarrhea	1 (1.9%)	2 (3.6%)	1 (1.4%)	2 (2.7%)	2 (0.02%)	4 (0.02%)
severe diarrhea	0	1 (1.8%)	0	0	0	1
explosive diarrhea	0	1 (1.8%)	0	0	0	1
indigestion	1 (1.9%)	0	0	0	1	0
headache	1 (1.9%)	2 (3.6%)	0	1 (1.4%)	1 (0.004%)	3 (0.01%)
dizziness	1 (1.9%)	0	0	0	1	0
alopecia	0	0	0	0	0	0
rash	0	1 (1.8%)	0	1 (1.4%)	0	2

Impression:

- The frequency of these selected ADR's is low. This medical reviewer agrees with the 1991 medical reviewer that there is no statistically or clinically significant difference between treatment groups. However, there is always a chance that the sample size is too small to provide the power to demonstrate a difference.
- The remaining ADR's that were reported by the sponsor in the pivotal studies but not presented in this review either occurred only in a patient taking placebo or the difference between treatment groups was not statistically or clinically significant.

3.3.4 Laboratory Test Abnormalities

- Minimal information regarding laboratory test abnormalities was provided in the original medical review (attempts by the CSO to locate additional laboratory safety summaries have been unsuccessful to date). According to that medical review, "no severe deviations from the baseline were observed" but there were some statistically significant changes:

Study 001

monocytes-
calcium-

1.45% mean increase from baseline in the Elmiron group
0.19% mean increase from baseline in the Elmiron group

Study 002: aPTT and calcium (the % change from baseline was not provided)

Overall Impression of the Pivotal Safety Data

- The safety monitoring in the pivotal studies appears to have been sufficient.
- The pivotal studies did not demonstrate any serious ADR's or deaths.
- The use of Elmiron was not associated with a statistically or clinically significant treatment group difference for any ADR, and was not associated with a clinically significant treatment group difference for any laboratory test abnormalities. It is difficult to make further conclusions about the laboratory test abnormalities, however, because of the limited available information. For a similar reason, this reviewer cannot determine the precise time of each ADR occurrence during the 3 month study.
- By comparison with related drugs such as Hemoclar, bleeding- or thrombotic-associated ADR's were not seen with the use of Elmiron.
- By body system, the most common ADR's are gastrointestinal in nature.
- Demographic analyses based on gender, age and race were not done (males comprised <1% of the study population).
- This placebo-controlled safety database demonstrates that Elmiron is safe to administer to this disease population at a dose of 100 mg orally TID for 3 months.

3.4 *Compassionate Use Study*

3.4.1 *Introduction*

- Since 1986, Elmiron has been available from the sponsor on a compassionate use basis. As of December 31, 1994, 2506 patients with IC have received Elmiron (the sponsor's database contains data up to this date except where noted).

Study Design

- open-label, unblinded and non-placebo controlled
- the inclusion/exclusion criteria parallel those used in the pivotal studies and are reasonable
- dose: 100 mg orally 3x a day (the drug was dispensed as a 3-month supply- the patient had to contact the investigator to arrange for the next shipment); this reviewer is uncertain if the to-be-marketed formulation was used solely

- **safety assessment:** a physical examination, an ADR assessment (where the investigator asks the patient if any ADR's have occurred) and an appropriate battery of laboratory tests were checked at baseline and presumably at every 3 month interval when the patient asked for another supply of Elmiron

Results to date (this study is on-going)

- **range of duration of patient study participation:** up to ~8 years
- **drop-outs:** the sponsor states that 211 patients as of December, 1994 have dropped out due to an ADR; the most common ADR's were alopecia (31 patients), diarrhea (30 patients) and nausea (24 patients); the sponsor has been asked to submit much more information regarding these drop-outs prior to a final decision on this NDA

3.4.2 Death Reports

- The sponsor submitted the reports of 6 deaths from 1986 to October, 1995.

Table 3: Death Reports Submitted during the Compassionate Use Study
(adapted from Appendix F of the August 31, 1995 amendment and an October, 1995 MedWatch report; n = ~2700 because it comprises patients in the study through June, 1995)

ADR	Duration of Elmiron Use	Clinical History	Investigator's Opinion of Relation to Elmiron Use
death	8 months (3/91 - 11/91)	55 male w/ history of metastatic melanoma. Death occurred in 2/92	unrelated
death	4/92 to ?	72 male w/ history of hypertension, cardiovascular disease suffered a stroke and died in 1992 (date not provided).	unknown
death	30 months (1/91 - 7/93)	75 female w/ history of hypertension was diagnosed w/, & died 1/93 (?) of, poorly differentiated metastatic adenocarcinoma	remote
death	3 months (9/93 - 12/93)	74 female died 4 weeks post-gastroplasty/hiatal hernia repair; Elmiron stopped 2.5 months prior to surgery and not restarted	unrelated
death	75 months (1987 - 4/94)	68 female died of metastatic bronchogenic carcinoma; no hemorrhage	unrelated
death*	~16 months (3/94 - 6/95)	67 male w/ history of hypertension, ischemic heart disease, arrhythmias; meds- Procardia, Catapres, Inderal; died in 7/95- exact cause of death unknown	pending

Legend: * MedWatch report; Amendment 57 to IND

October 4, 1995

Impression

- This reviewer agrees with the sponsor that the death of Patients 1, 4 and 5 is unrelated to Elmiron use. The death of Patient 3 was most likely unrelated to Elmiron.
- It is impossible to state anything certain about Patient 2 except that he had risk factors for stroke.
- Although the exact cause of death for Patient 6 is unknown, the clinical history highly suggests a cardiovascular etiology.
- The above reports (representing 6 out of ~2700 patients) do not suggest a connection to Elmiron.

3.4.3 *Serious Reports of Adverse Drug Reaction*

- The sponsor reports that 33 serious ADR's occurred from 1986 to June, 1995. In lieu of an actual case report form, the sponsor submitted a brief synopsis of the clinical history, duration of Elmiron use and the investigator's opinion regarding the relation of Elmiron to the ADR. *(Please see Appendix D of this review.)*
- After reviewing these 33 ADR synopses, this medical reviewer selected only those reports that are most likely to have been related to the use of Elmiron (Table 4).

Table 4: Selected Listing of Serious Reports of Adverse Drug Reaction
 (selected by this reviewer based on likelihood of a relationship to Elmiron; adapted from Appendix F; n = ~2700)

ADR	Duration of Elmiron Use	Clinical History	Investigator's Opinion of Relation to Elmiron Use
diarrhea & dehydration	4 months (5/93 - 9/93)	34 female w/ no history of GI problems was hospitalized for 5 days due to severe diarrhea (4-6 watery stools/day) & dehydration; past history & complete GI evaluation were negative; meds- imipramine, Motrin, Percocet. Elmiron stopped; diarrhea resolved w/ IV fluids and dietary support. Elmiron not restarted.	possible
abdominal pain	3 months (2/94 - 5/94)	81 female hospitalized w/ increasing severe abdominal pain with sporadic diarrhea w/o emesis or nausea. Meds- Desyrel, Paxil, Librax, Klonopin, Mevacor, Doxepin, Lomotil, Vicodin, Premarin, Provera. Diagnosed w/ cholelithiasis; discharged w/o symptoms	unrelated

Impression

- These 2 serious ADR's could very possibly have been related to the use of Elmiron. Gastrointestinal side effects with Elmiron use have been well documented, although they typically are not so severe as to require hospitalization. Interstitial cystitis has been associated with inflammatory bowel disorders in some patients. In fact, one recent epidemiologic study found irritable bowel syndrome, frequent stools and spastic colon to be potential risk factors associated more often with patients with IC versus a control population (and the difference between the groups was markedly statistically significant).⁴ These patients may be prone to more severe gastrointestinal ADR's. Certainly patients with a history of GI problems such as inflammatory bowel disease, irritable bowel disease, and gallbladder disease will have to be watched carefully. This should be reflected in the labeling if Elmiron is approved.
- The gastrointestinal toxicity found with the use of Elmiron can and should be further monitored during Phase 4 if Elmiron is approved. There is a need to determine which patients have gastrointestinal toxicity due to the drug or due to the bowel disorder (or both). At this time, the contribution of concomitant medications can also be examined.

3.4.4 General Reports of Adverse Drug Reactions

Table 5: ADR's Reported in the Compassionate Use Database with ≥ 1% Incidence
(adapted from the December 1, 1995 amendment; arranged by decreasing frequency)

ADR	Patients (n = 2506)		Maximum Severity				Related to Elmiron?			Elmiron Continued?		
	#	%	Mild	Mod	Sev	Unk	Yes	No	Unk	Yes	No	Unk
alopecia		3.9	17	21	3	57	60	9	29	44	52	2
diarrhea		3.9	19	18	8	53	67	8	23	47	44	7
nausea		3.7	12	17	11	53	60	11	22	40	47	6
headache		2.8	6	17	5	42	40	15	15	34	35	1
rash		2.6	8	6	4	46	34	11	19	27	35	2
dyspepsia		2.2	8	11	5	31	27	9	19	20	30	5
abdominal pain		2.0	6	9	1	32	22	9	20	16	30	5
pain (location not specified)		2	1	8	10	31	17	18	15	24	24	2
dizziness		1.1	0	6	3	19	20	3	5	10	17	1
enia		1.1	3	5	2	17	14	4	9	16	10	1
LFT abnormality		1	6	4	0	16	17	1	8	10	15	1

Impression:

- The safety monitoring appears to have been as adequate as possible for an outpatient study. Reports of ADR's could have been lost due to the high drop-out rate (the drop-out rate is demonstrated in the efficacy review, Section 4.0).
- Of the 11 ADR's with a frequency of $\geq 1\%$, 4 (perhaps 5) concern the gastrointestinal system (diarrhea, nausea, dyspepsia, and LFT abnormality; abdominal pain could have a gynecologic or renal etiology instead of a gastrointestinal origin).
 - The diarrhea, nausea, dyspepsia and abdominal pain could be due to an "osmotic" load effect of the Elmiron created by undigested and/or unabsorbed PPS molecules (and the cellulose that is part of the capsule).
- Despite the clustering of multiple ADR's to 1 body system, the overall frequency is still acceptably low and the reader must remember that concurrent gastrointestinal conditions may confound the picture.
 - A lack of serious or severe gastrointestinal toxicity in Phase 1 studies (even at a dosage of 400 mg TID orally) is reassuring.
- The 3.9% incidence of alopecia is very interesting given the similarity of Elmiron to LMW heparin and the rare association of this ADR with heparin therapy. An autoimmune component is the probable mechanism. Given the nonfatal nature of this ADR and the low frequency, the occurrence of this side effect during Elmiron therapy is tolerable from a regulatory perspective.
- Clearly, the investigators believe that Elmiron was involved with the ADR (with the exception of the nonspecific category "pain") although there was a not insignificant percentage of "unknown" replies to the question of relationship to Elmiron.
- Despite a definite trend in the opinion of Elmiron's relationship to an ADR, the continuation of Elmiron therapy was more evenly split. Obviously, unless the ADR is serious and/or severe enough, each patient will decide if the Elmiron benefit is worth the ADR.
- The large number of ADR's reported as "unknown" severity is disconcerting; it comprises >50% of the reports for most of the ADR's. The sponsor was questioned on this finding and the reply was that some investigators simply did not designate the severity of the ADR in the case report form, although that question was specifically asked.
- Table 6 presents the percentage of patients reporting the ADR as mild, moderate or severe after excluding the "unknown" reports. The recalculation of the

percentage provides a better picture of the number of patients reporting the severity of the ADR.

Table 6: A Revised Examination of the Number and Percentage of Each ADR by Severity

ADR	# ADR Reports with a Severity Rating	Maximum Severity for each ADR calculated after subtracting out # of unknowns from the total number of reports) (# and [%])		
		Mild	Mod	Sev
alopecia	41	17 (40)	21 (50)	3 (10)
diarrhea	45	19 (40)	18 (40)	8 (20)
nausea	40	12 (30)	17 (40)	11 (30)
headache	28	6 (20)	17 (60)	5 (20)
rash	18	8 (40)	6 (30)	4 (20)
dyspepsia	24	8 (30)	11 (50)	5 (20)
abdominal pain	16	6 (38)	9 (56)	1 (6)
pain (location not specified)	19	1 (5)	8 (42)	10 (52)
dizziness	9	0 (0)	6 (70)	3 (30)
asthenia	10	3 (30)	5 (50)	2 (20)
LFT abnormality	10	6 (60)	4 (40)	0 (0)

Impression:

- Once again with the exception of the nonspecific "pain" category, most patients reported the severity of the ADR as either mild or moderate.
-
- For the sake of completeness, Table 7 presents select ADR's that occurred with < 1% frequency but could have significant clinical ramifications if severe.

Table 7: Select ADR's Reported in the Compassionate Use Database with Incidence < 1%
(Excerpted by this reviewer based on importance of ADR; arranged by decreasing incidence)

ADR	Patients (n = 2506)		Maximum Severity				Related to Elmiron?			Elmiron Continued?		
	#	%	Mild	Mod	Sev	Unk	Yes	No	Unk	Yes	No	Unk
ecchymosis		0.72	8	2	0	8	11	3	4	6	11	1
hematuria		0.52	2	3	0	8	4	5	4	6	7	0
epistaxis		0.32	2	0	1	5	5	0	3	1	7	0
SGOT elevated		0.28	0	1	0	6	1	2	4	3	4	0
SGPT elevated		0.24	1	2	0	3	4	1	1	1	5	0
thrombocytopenia		0.24	1	0	0	5	0	0	6	2	4	0
allergic reaction		0.24	1	1	0	3	3	2	0	2	3	0
death		0.12	0	0	1	2	0	3	0	0	3	0
face edema		0.12	1	0	0	2	2	0	1	1	2	0
generalized edema		0.04	0	0	0	1	0	0	1	0	1	0

Impression:

- Once again, the safety monitoring appears to have been as adequate as possible for an outpatient study.
- There is a hint of a bleeding tendency (ecchymosis, hematuria, epistaxis) but a quick look at the reports with known severity shows that most were mild or moderate. The role of concomitant diseases must be considered. For example, the hematuria may have been entirely due to the interstitial cystitis. The lack of reports of serious bleeding is reassuring.
- The lack of an alteration in the coagulation scheme laboratory tests (i.e. an increased PT, aPTT and/or bleeding time) in the Phase 1 studies using a dose of 100 mg TID orally is also reassuring.
- Similarly there is a hint of an allergic reaction to Elmiron in some patients but this is not unexpected and, with the exception of rash (reported in Table 6), the number of reports is very small. The role of concomitant diseases must also be considered here. Overall, the frequency of these ADR's is not alarming.
- With the large sample size in this study, it is reassuring to see a < 1% frequency of thrombocytopenia given Elmiron's chemical similarity to LMW heparin. As stated previously Section 3.2.1.1, the current frequency of

thrombocytopenia with LMW heparin is less than 10%.

- As before, some ADR's are primarily reported with an unknown rating of severity. The total number of reports for each ADR are small however, particularly for the allergic-type ADR's.

(To provide a complete picture of the data, the above 2 tables were combined into 1 table with the ADR's grouped by body system [please see Appendix B].

- Another look at the safety database, now by time of occurrence, is warranted since the anticipated minimum duration of drug use in the label indication is 3 months:

Table 8: Number and Percentage of Selected ADR's Reported in the Compassionate Use Study-- Presented by Time of Occurrence (n = 2506)

(adapted from the December 11, 1995 amendment; specific ADR's selected by this reviewer to correspond with the above tables; listed by decreasing incidence at the 3 month time interval)

ADR	WEEKS 1-4		WEEKS 5-8		WEEKS 9-12		MONTHS 0-3		MONTHS 0-6		MONTHS 0-12	
	#	%	#	%	#	%	#	%	#	%	#	%
NAUSEA	51	2.04	15	0.60	4	0.16	70	2.79	82	3.27	88	3.51
DIARRHEA	41	1.64	13	0.52	9	0.36	65	2.59	78	3.11	86	3.43
HEADACHE	33	1.32	9	0.36	8	0.32	51	2.04	60	2.39	64	2.55
ALOPECIA	28	1.12	9	0.36	7	0.28	47	1.88	64	2.55	77	3.07
RASH	32	1.28	8	0.32	5	0.20	45	1.80	53	2.11	53	2.11
ABDOMINAL PAIN	30	1.2	5	0.20	7	0.28	43	1.72	48	1.92	49	1.96
DYSPEPSIA	23	0.92	5	0.20	3	0.12	33	1.32	40	1.60	47	1.88
PAIN	17	0.68	5	0.20	4	0.16	28	1.12	37	1.48	42	1.68
DIZZINESS	10	0.4	4	0.16	1	0.04	16	0.64	22	0.88	24	0.96
ASTHENIA	9	0.36	3	0.12	1	0.04	13	0.52	19	0.76	24	0.96
ECCHYMOSIS	5	0.2	2	0.08	3	0.12	10	0.40	12	0.48	14	0.56
HEMATURIA	3	0.12	2	0.08	2	0.08	7	0.28	8	0.32	11	0.44
LFT ABNORMAL	1	0.04	0	0.00	3	0.12	4	0.16	6	0.24	11	0.44
ALLERGIC REACTION	1	0.04	1	0.04	1	0.04	3	0.12	4	0.16	5	0.20
EPISTAXIS	0	0	0	0.00	2	0.08	2	0.08	4	0.16	6	0.24
THROMBOCYTOPENIA	1	0.04	0	0.00	0	0.00	1	0.04	1	0.04	1	0.04
SGOT INCREASED	1	0.04	0	0.00	0	0.00	1	0.04	3	0.12	3	0.12
SGPT INCREASED	0	0	0	0.00	1	0.04	1	0.04	2	0.08	2	0.08
DEATH	0	0	0	0.00	0	0.00	0	0.00	0	0.00	3	0.12
FACE EDEMA	0	0	0	0.00	0	0.00	0	0.00	1	0.04	1	0.04
GENERALIZED EDEMA	0	0	0	0.00	0	0.00	0	0.00	1	0.04	1	0.04
HEMORRHAGE	0	0	0	0.00	0	0.00	0	0.00	0	0.00	1	0.04

Impression:

- Table 8 demonstrates that the most likely ADR's during the first 3 months are gastrointestinal in nature (nausea, diarrhea, abdominal pain and dyspepsia). As (reported in Table 5), only 2 out of ~2700 patients were reported to have had GI side effects severe enough to warrant hospitalization. This is an acceptable frequency.
- Overall, the ADR profile of Elmiron is benign during the first 3 months of therapy. As demonstrated by the absolute number of patients experiencing each ADR, the frequency does not increase to a clinically significant extent when the patient is receiving the drug for up to a year.

3.4.5 Laboratory Test Abnormalities

- Details regarding the changes in laboratory parameters for individual subjects were not reported in this NDA. Summary statistics also were not provided.

3.5 Other Studies in the United States

- This information was submitted in an annual report for IND dated May 2, 1995 and encompasses the period from January 1, 1994 to December 31, 1994.
-
- Clinical Pharmacology of Pentosan Polysulfate Sodium Administered via Oral, Subcutaneous and Intravenous Routes (Protocol #IX 107-063)
 - IND Georgetown University, Washington, DC

Pertinent study design details

- open-label; healthy volunteers (clinical pharmacology) and cancer patients (long-term safety and tolerance)
- dose: not provided for the clinical pharmacology section; 900, 2040 or 3060 mg TID orally for the cancer patients

Results

- Healthy volunteers: no ADR's reported, no drop-outs; PK/PD data not provided
- Cancer patients: 2 of 13 drop-outs were due to ADR (severe diarrhea

and positive stool guaiac); 1 patient was taking 2040 mg TID and the other was taking 3060 mg TID

Impression

- The magnitude of the dose for these ADR's precludes a reasonable direct comparison to the dose used in patients with IC.
- Numerous ongoing open-label protocols for patients with radiation cystitis.

The details regarding the number of drop-outs and/or ADR's were not reported by the sponsor.

3.6 *Foreign Studies*

- The following information was reported in the Annual Report for IND (Amendment 53) on May 2, 1995.
- CTX00530-0393-A/Protocol #IX 104-063I: A Double Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Oral Pentosan Polysulfate Sodium [Elmiron] in Patients with Interstitial Cystitis

This a double-blind study being conducted in the United Kingdom. So far 97 patients have entered the study. Three ADR's were reported as serious and/or unexpected:

Table 9: Serious Adverse Drug Reaction Reports during a Double-blind Study in the United Kingdom

(excerpted from an annual report for IND (Amendment 53) dated May 2, 1995 but this information was also listed in the August, 1995 NDA amendment)

ADR	Dose/Duration	Clinical History	Investigator's Opinion of Relation to Elmiron
weakness, confusion	Elmiron 200 mg TID orally/ 3 months (blind broken)	80 female w/ history of thyroid cancer. In 6/93, noted to have increasing weakness/confusion. Liver ultrasound showed metastatic cancer. Elmiron stopped 5/93; death in 7/93	unrelated
hemoptysis	Elmiron 200 mg TID orally/ 3 months (blind broken)	58 female w/ history of bronchiectasis w/ hemoptysis. 3 weeks of fever, chills & sore throat. Elmiron stopped on admission.	unrelated
hemiplegia	Placebo/ 2 months (blind broken)	73 female w/ history of hypertension, myocardial infarction was admitted w/ hemiplegia; PT/PTT normal. Elmiron stopped day before admission.	unrelated

Impression:

- The case report form for each ADR was reviewed and this reviewer agrees with the investigators' assessment that these ADR's were unrelated to Elmiron.
- In addition to the above 3 ADR's, 10 more subjects were discontinued due to an ADR but the blind has not been broken for these subjects.

-
- Protocol #IX 103-063I: A Double-blind, Placebo Controlled Pilot "Evaluation of the Safety and Efficacy of Oral Pentosan Polysulfate Sodium for the Relief of Symptoms in Patients with Chronic Abacterial Prostatitis or Prostatodynia

This study is also being conducted in the United Kingdom. There has been 1 drop-out due to an ADR (generalized itching) out of 8 patients entered. This ADR may very well be an allergic reaction to Elmiron but a final determination is not possible until the blind is broken.

- Protocol #IX 114-063: A Compassionate, One Year, Open-Label Evaluation of the Safety and Efficacy of Oral Pentosan Polysulfate Sodium for the Relief of Symptoms in Patients with Interstitial Cystitis

In this study each subject who completed the double-blind study above could elect to receive 200 mg TID orally. There have been 2 drop-outs due to an ADR (tooth abscess, and urinary retention) out of 14 patients entered. These ADR's are unlikely to be related to Elmiron.

3.7 Overall Impression of Safety

- The complete safety database for this NDA is based on a sample size of almost 3000 patients with interstitial cystitis.
 - In general, the methodology employed to assess the safety of this product was reasonable.
- At a dose of 100 mg administered orally three times a day, Elmiron appears to be relatively free of major and severe toxicity.
- The number of deaths seen in the pivotal and Compassionate Use studies comprised a very low percentage of the total number of patients who have taken Elmiron. In addition, there does not appear to be a link between these deaths and Elmiron.
- There were no reports of serious ADR's in the pivotal studies. Of the 33 reports of serious ADR's from the Compassionate Use study, this reviewer believes that only 2 are most likely to be due to the Elmiron. It is reassuring that these 2 ADR's represent < 1% of the total safety database. The 3 serious ADR reports from the United Kingdom were unrelated to Elmiron use.
- By body system, gastrointestinal adverse events such as diarrhea, nausea, and dyspepsia were most frequently associated with Elmiron use. In general, these symptoms were reported as mild but the 2 serious ADR reports noted above were gastrointestinal in nature. Certainly patients with a history of GI problems such as inflammatory bowel disease, and gallstone disease will have to be watched carefully. This should be reflected in the labeling if Elmiron is approved for marketing.
- The gastrointestinal toxicity found with the use of Elmiron can be further monitored during Phase 4 if Elmiron is approved. In particular, interstitial cystitis has been associated with inflammatory bowel disorders in some patients hence there is a

need to determine which patients have gastrointestinal toxicity due to the drug or due to the bowel disorder (or both). The role of concomitant medication (which is the usual status for patients with interstitial cystitis) can also be studied.

- There is no hint of any statistically or clinically significant thrombocytopenic complications. There are some occurrences of minor bleeding complications and perhaps an allergic response associated with the use of Elmiron but the numbers are too small to definitively relate them directly to Elmiron.
- Alopecia was seen in 3.9% of the patients in the Compassionate Use study but not in any of the patients in the pivotal studies. This adverse event is most likely autoimmune in nature and certainly not life-threatening.
- Specific details regarding any laboratory test abnormalities are lacking at this time and will be evaluated once the full safety database for the Compassionate Use study is submitted.
- As opposed to the original pivotal studies which were conducted for 3 months each, the Compassionate Use study also examined the long-term use of Elmiron. The overall adverse event profile for Elmiron is benign during the first 3 months of therapy. As demonstrated by the absolute number of patients experiencing each ADR, the frequency does not increase to a clinically significant extent when the patient is receiving the drug for up to a year.
- This reviewer acknowledges that the Compassionate Use study generated uncontrolled safety data, and the pivotal study safety database is small. The uncontrolled database is of a good size, however, and the ADR frequencies are small.
- A demographic subset analysis of the safety database (by age, gender, race, and severity of disease at baseline) was not performed by the sponsor but can be requested in the action letter.
- Based on the information submitted to the FDA thus far, this reviewer is comfortable with the safety profile of Elmiron. This opinion may change, if warranted, after review of the pending submission containing a database of discontinuations due to an adverse event, and case report forms.

4.0 EFFICACY REVIEW

- In Appendix C please see Table 1 for an overall summary of the patient enrollment and discontinuation.

4.1 *Pivotal Studies*

- As discussed above in Section 1.2 under the heading "October 28, 1994", the FDA found that study 002 was adequate and well-controlled and therefore would provide some evidence of efficacy (overall improvement based on investigator evaluation [global], and improvement in bladder pain based on patient overall assessment [global]).

4.2 *Compassionate Use Study*

- The motivation behind the sponsor submitting this compassionate use data is so that the study could be evaluated and possibly considered as a second pivotal trial. If this study is accepted in place of an additional adequate and well-controlled trial and the results support the efficacy and safety of Elmiron, this submission will fulfill the regulatory requirement of replication of study results. The FDA agreed to accept this submission and consider it in this capacity.

Study Design

- The Compassionate Use program for Elmiron was established in 1986 for patients with interstitial cystitis (IC). Certain eligibility criteria were evaluated before a patient could be enrolled in this program. Patients were required to undergo cystoscopic evaluation with bladder biopsy and urinary cytology and to meet specific IC diagnostic inclusion criteria of having bladder glomerulations, Hunner's ulcers and symptoms of bladder pain and/or urgency. Patients with bacterial cystitis, genitourinary tuberculosis, radiation cystitis, bladder carcinoma, or neurogenic bladder were excluded as these diseases may mimic the symptoms of IC.
- Several urological and symptomatic parameters were rated by the patients at baseline. Demographic information and laboratory evaluations were also recorded at baseline.
- For the Compassionate Use program, Elmiron was dispensed in three-month supplies. Therefore, since reordering was necessary every three months, patients were evaluated in three month intervals as long as they continued to participate in the program. Efficacy (overall change in IC, overall change in pain, overall change in urgency, pain discomfort score, pressure to urinate, frequency, and nocturia), laboratory (hematology,

coagulation, chemistry, urinalysis, and urine pregnancy test), and safety (monitored adverse events) data were obtained at each reorder visit. Patients were required to pay for the drug and generally were not reimbursed by insurance. If a patient dropped out of the study, the reason for withdrawal was supposed to be noted on the case report form.

- Although the consistency and rigor with which patients were entered and data was collected in this program is similar to what might be done in a controlled clinical trial, it should be noted that both the patients and physicians were completely unblinded and no control group was involved. Consequently, there are no statistical procedures which can be used to unequivocally assess whether the outcomes seen in this data are a result of the placebo effect or of the use of Elmiron.

Data Analysis

Patient Baseline Status

- Approximately 2700 patients have been enrolled in the Elmiron Compassionate Use Program since 1986. Table 1 in Appendix A includes the distribution of age and gender by the patients' length of participation in the Compassionate Use Program. For this table, patients were divided into three groups: patients who merely entered the Compassionate Use Program but who ordered Elmiron at least once, patients who continued in the program for at least three months, and patients who continued for at least one year. Race was not included in this table since over 95% of the compassionate use patients were white. No significant differences in baseline characteristics were observed in patients who merely entered the program versus patients who continued to participate in the program for at least three months or at least one year. The only apparent imbalance in the distribution of patients is that approximately 90% of the patients (at entry as well as at three months and one year) were female. However, considering the characteristics of the disease being treated, this seems appropriate.
- Table 2 in Appendix A contains patients stratified by their baseline disease status. The disease status parameters included in this table are disease duration, severity of drainage, fissures, petechial hemorrhages, hunner's ulcers, baseline pain/discomfort score, baseline urgency, baseline frequency, and baseline nocturia. No significant differences in disease status were observed comparing all patients who entered the program to patients who continued to participate in the program for at least three months or for at least one year.

Flowchart of Total Length of Participation

- Table 10 illustrates patients' length of participation in the Compassionate Use program as well as the number of patients who dropped out of the program. The *Active Patients* include two types of subjects: (i) *Proceeding Patients* which is defined as those patients who continued in the program beyond the current time interval and (ii) *Young Patients* which is defined as those patients who are currently taking Elmiron but are too young in the program to be included in the next time interval. Inactive patients are patients who have not reordered Elmiron at their most recent tri-monthly opportunity but who have not been formally discontinued from the program. Discontinued patients are patients who have formally discontinued using Elmiron. More discussion of Table 10 follows the table. Patients' reasons for discontinuation are listed in Table 11.

Table 10 : Distribution of Patient Status by Total Length of Participation

Total Length of Participation	Cumulative Total Number of Patients	Active Patients		Inactive Patients	Discontinued Patients ¹
		Proceeding	"Young" Patients		
0 < x ≤ 3 mo.	2499	1192 (47.70%)	174	69	1064
3 < x ≤ 6 mo.	1192	892 (35.69%)	76	9	215
6 < x ≤ 12 mo.	892	598 (23.93%)	68	16	210
12 < x ≤ 18 mo.	598	461 (18.45%)	34	6	97
18 < x ≤ 24 mo.	461	355 (14.21%)	40	5	61
24 < x ≤ 36 mo.	355	225 (9.00%)	53	7	70
36 < x ≤ 48 mo.	225	145 (5.80%)	47	7	26
48 < x ≤ 60 mo.	145	86 (3.44%)	37	3	19
60 < x ≤ 90 mo.	86	0 ² (0.00%)	72	6	8
Total	NA	NA	601 (24.05%)	128 (5.12%)	1770 (70.83%)

1. The reasons for discontinuation are described in Table 11.

2. The number of patients proceeding to the next time interval was confined to being zero because although the compassionate use program is continuing, the data set had to be truncated at 90 months after the first patient was enrolled in order for analysis to be conducted.

- Elmiron appears (due to the subjects continued participation in the program) to be having an effect for approximately 25% of IC patients shown in the 'Young Patients' column in Table 10. The remaining 75% of IC patients listed in the inactive or discontinued columns seem not to experience a clear effect from Elmiron use. The subjects' reasons for discontinuation are in Table 11.

Table 11: Reasons for Discontinuation

Total Length of Participation	Number of Discontinued Patients	Reasons for Discontinuation				
		Adverse Event	Failed to Return	Death	Lack of Efficacy	Other*
0 < x ≤ 3 mo.	1064	218 (20.49%)	71 (6.67%)	0 (0.0%)	344 (32.33%)	407 (38.25%)
3 < x ≤ 6 mo.	215	22 (10.23%)	11 (5.12%)	1 (0.47%)	83 (38.60%)	95 (44.19%)
6 < x ≤ 12 mo.	210	20 (9.52%)	15 (7.14%)	0 (0.0%)	73 (34.76%)	98 (46.67%)
12 < x ≤ 18 mo.	97	14 (14.43%)	9 (9.28%)	1 (1.03%)	23 (23.71%)	45 (46.39%)
18 < x ≤ 24 mo.	61	9 (14.75%)	3 (4.92%)	0 (0.0%)	15 (24.59%)	32 (52.46%)
24 < x ≤ 36 mo.	70	12 (17.14%)	6 (8.57%)	3 (4.29%)	13 (18.57%)	34 (48.57%)
36 < x ≤ 48 mo.	26	7 (26.92%)	6 (23.08%)	0 (0.0%)	1 (0.04%)	11 (42.31%)
48 < x ≤ 60 mo.	19	3 (15.79%)	1 (5.26%)	0 (0.0%)	1 (5.26%)	13 (68.42%)
60 < x ≤ 90 mo.	8	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	7 (87.5%)
Total	1770	305 (17.23%)	122 (6.89%)	5 (0.28%)	554 (31.30%)	742 (41.92%)

* includes administrative and financial reasons

An Attempt to Predict a Responder Versus a Nonresponder

- At the request of FDA, the sponsor made an attempt to identify baseline characteristic(s) which could be used to predict an IC patient's classification as "responder" or "non-responder". It should be noted that this analysis was carried out for exploratory purposes only and the results would need to be replicated before being accepted as part of the efficacy profile of Elmiron. For this analysis, patients were classified as *responders* if they continued in the program for at least a year and graded their overall change in IC as moderate or greater improvement. Patients who dropped out of the program before participating at least one year or who rated their overall change in IC as slight or less were considered *non-responders*. The following parameters were considered possible

predictors of responder/non-responder status: age, sex, disease duration, severity of drainage, fissures, linear scars and glomerulations, petechial hemorrhages, Hunner's ulcers, baseline pain/discomfort score, baseline urgency, baseline frequency, and baseline nocturia. Race was not included since over 95% of the patients were white. Of the parameters listed, baseline nocturia ($p=0.0288$) was the only factor which was identified as being potentially important for predicting patients' responses to Elmiron. The analysis indicated that the less severe a patient's baseline nocturia is, the more likely that patient is to be in the Elmiron responder group. (One should note however that 13 variables were evaluated in this analysis and that if a Bonferroni multicomparison procedure was applied, the p -values associated with nocturia would be considered non-significant.)

Efficacy Analysis by Length of Participation

- The sponsor analyzed the Elmiron compassionate use data in accordance with an analysis plan developed by FDA. This retrospectively designed analysis plan carries with it certain biases. However, the analysis plan was designed by FDA statisticians without knowledge of the data. This should eliminate the concern that several analyses may have been conducted but only the "best" analysis was submitted. The data has been acquired over an extended period of time and therefore, most likely we are seeing the results of the Elmiron responder group and not the entire sample of IC patients.
- The compassionate use efficacy data was organized into three groups for the analysis of the responder population. The first group consists of all patients who participated in the Compassionate Use program for at least one year. The second group consists of all patients who participated for at least two years. And finally, the third group includes all patients who were involved for at least three years. Note that these groups are not disjoint. Tables 12a, b, and c contain the medians, means, and confidence intervals for each of the seven efficacy parameters in each of the analysis groups. A discussion of the efficacy parameters and the implications which can be drawn from them follows each of the tables. Clinically significant changes in the efficacy parameters were not specified *a priori*. Similarly, primary efficacy endpoints were not declared *a priori*; however, the change in pain was deemed by Jean Fourcroy, MD² to be the most important parameter measured.

Table 12a: Change in Efficacy Parameters from Baseline to the Patient's Final Measurement (within the 1, 2, and 3 year restrictions)

Efficacy Parameter ²	At least One Year of Participation	At least Two Years of Participation	At least Three Years of Participation
Patient's Rating of Overall Change in IC ¹	N = 516 Median = 4.0 Mean = 4.25 CI: (4.16, 4.34)	N = 262 Median = 5.0 Mean = 4.43 CI: (4.32, 4.54)	N = 132 Median = 5.0 Mean = 4.55 CI: (4.41, 4.68)
Patient's Rating of Overall Change in Pain ¹	N = 516 Median = 4.0 Mean = 4.26 CI: (4.17, 4.36)	N = 262 Median = 5.0 Mean = 4.45 CI: (4.32, 4.57)	N = 132 Median = 5.0 Mean = 4.52 CI: (4.36, 4.69)
Patient's Rating of Overall Change in Urgency ¹	N = 515 Median = 4.0 Mean = 4.12 CI: (4.03, 4.22)	N = 262 Median = 5.0 Mean = 4.31 CI: (4.19, 4.43)	N = 131 Median = 5.0 Mean = 4.44 CI: (4.28, 4.60)

1. Measured on a six point scale: 1=worse, 2=no better, 3=slightly improved, 4=moderately improved, 5=greatly improved, 6=symptom gone

2. The Wilcoxin Signed Rank Test showed that in all three data analysis groups, all efficacy parameters were statistically significantly different from the 'no-change-from-baseline' category (p<0.001).

- Table 12a shows that on average, the patients' ratings of their overall change in IC, pain, and urgency was between "moderately improved" and "greatly improved". This was statistically significantly different from the "no better" category (p<0.001).

Table 12b: Change in Efficacy Parameters from Baseline to the Patient's Final Measurement (within the 1, 2, and 3 year restrictions)

Efficacy Parameter ³	At least One Year of Participation	At least Two Years of Participation	At least Three Years of Participation
Pain/Discomfort Score ¹ (=Baseline - Final Measurement)	N = 500 Median = 1.0 Mean = 0.80 CI: (0.72, 0.87)	N = 252 Median = 1.0 Mean = 0.92 CI: (0.82, 1.01)	N = 126 Median = 1.0 Mean = 1.02 CI: (0.89, 1.16)
Pressure to Urinate ² (Urgency) (=Baseline - Final Measurement)	N = 521 Median = 1.0 Mean = 0.87 CI: (0.78, 0.96)	N = 258 Median = 1.0 Mean = 1.03 CI: (0.91, 1.16)	N = 125 Median = 1.0 Mean = 1.17 CI: (1.00, 1.34)

1. Measured on a 10 point scale. Collapsed at the request of FDA to a three point scale:
1=none/mild, 2=moderate, 3=severe/unbearable
2. Measured on a four point scale: 1=none, 2=mild, 3=moderate, 4=severe
3. The Wilcoxin Signed Rank Test showed that in all three data analysis groups, all efficacy parameters were statistically significantly different from the 'no-change-from-baseline' category ($p < 0.001$).

- From Table 12b, we see that subjects' ratings of their pain/discomfort and pressure to urinate dropped on average approximately one category. This drop is statistically significantly different from no change in the ratings ($p < 0.001$).

Table 12c: Change in Efficacy Parameters from Baseline to the Patient's Final Measurement (within the 1, 2, and 3 year restrictions)

Efficacy Parameter ²	At least One Year of Participation	At least Two Years of Participation	At least Three Years of Participation
Frequency of Urination ^{1, 3} (=Baseline - Final Measurement)	N = 500 Median = 3.0 Mean = 4.84 CI: (3.78, 5.91)	N = 246 Median = 3.0 Mean = 4.50 CI: (3.80, 5.93)	N = 122 Median = 4.0 Mean = 4.79 CI: (2.90, 6.67)
Frequency of Nocturia ¹ (=Baseline - Final Measurement)	N = 506 Median = 1.0 Mean = 1.94 CI: (1.53, 2.34)	N = 253 Median = 2.0 Mean = 2.09 CI: (1.43, 2.75)	N = 124 Median = 2.0 Mean = 2.52 CI: (1.86, 3.18)

1. Subject's estimated decreased number of occurrences per day (night)
2. The Wilcoxin Signed Rank Test showed that in all three data analysis groups, all efficacy parameters were statistically significantly different from the 'no-change-from-baseline' category ($p < 0.001$).
3. Extreme outliers which most likely were data entry errors were ignored ($n \approx 4$).

- As listed in Table 12c, the subjects' average reported frequency decreased by four to five occurrences. Similarly, the subjects' nocturia decreased by approximately two occurrences on average. Again, these changes are statistically significantly different from no change ($p < 0.001$).
- Although the overall changes in subjects' pain/discomfort, pressure to urinate, frequency of urination, and nocturia were positive in nature, when the data is stratified on the patients' baseline characteristics, this effect appears to be reversed in some cases. Table 3 in Appendix A contains the medians, means, and confidence intervals for the efficacy parameters where a reverse in effect is seen in the stratified data. The shaded regions represent the strata where a negative mean effect was observed. Generally, this reversal in effect was observed in the patients with mild baseline ratings. Not all of the negative results highlighted in Table 3 (Appendix A) are statistically significantly worse than baseline (ie. confidence interval is negative and does not contain zero). In fact, if an adjustment for multiple comparisons is made none of the results would be statistically significant. Although each of the negative results in Table 3 (Appendix A) is probably not important on its own, the overall trend in the data could prove to be important in patient management. The trend identified in Table 3 (Appendix A) suggests that a responder patient with milder baseline symptoms would be expected to experience a less dramatic improvement and possibly a slight deterioration in his or her

condition compared to a responder patient with severe baseline symptoms. In several cases where a patient reported mild baseline symptoms, worsening in the patient's reported conditions occurred.

Determination of an Adequate "Trial Period" for the Identification of Elmiron Responders

- Since no baseline characteristics have been identified which can predict whether a patient will be a responder or non-responder to Elmiron, most likely in clinical practice a "try-and-see" method of administration for Elmiron would be adopted. In the interest of patient management, an attempt was made to define the length of time which a patient or physician should "try" Elmiron before stopping treatment and classifying that patient as a non-responder to Elmiron. Tables 13a, b, and c are cross tabulations of the three month changes in the pain/discomfort score with six, nine, and twelve month changes in the pain/discomfort score. All changes in the pain/discomfort scores were obtained by subtracting the baseline ratings from the tri-monthly ratings. (Of the efficacy parameters collected, the pain/discomfort score was deemed by Jean Fourcroy, MD² as the most reliable measure of a patient's disease status and/or response to Elmiron.)
- The shaded regions in Tables 13a, b, and c contain the number of patients who reported a deterioration or no change (from baseline) in their pain/discomfort at three months and then reported an improvement (from baseline) at six, nine, or twelve months, respectively. For example in Table 13a, there were 116 / 879 (13.20%) patients who had no change or got worse at three months but who reported an improvement at six months. Therefore, if the "trial period" for Elmiron was set at three months, about 13% of patients would have been taken off Elmiron who might have seen some benefit after continued use for six months. Similarly in Table 13b, there are 93 / 633 (14.69%) patients who would be deemed non-responders at three months but who may have experienced some positive effect at nine months. In Table 13c, there are 65 / 421 (15.44%) patients who most likely would be taken off Elmiron at three months but may have experienced some improvement at 12 months. Although the number of patients in the shaded regions in Tables 13a, b, and c are decreasing, the proportion of patients in these regions is remaining fairly constant at about 14%. Therefore increasing the "trial period" for Elmiron to more than three months does not appear to increase the chances of identifying the portion of Elmiron responders who are possibly being missed. Although there is no way to substantiate it with the compassionate use data, it is possible that this 14% of patients are in question due to the waxing and waning of the symptoms of IC rather than a delayed response to Elmiron. In the opinion of these two

reviewers, three months is an adequate "trial period" for the identification of Elmiron responders.

Table 13a: Number of Subjects by each Level of Response (in Pain/Discomfort Rating) to Elmiron at Three Months Versus the Reported Response at 6 Months

Change (from Baseline) in Pain / Discomfort Score at Six Months					
Change (from Baseline) in Pain / Discomfort Score at Three Months		Deteriorated by 1 or 2 categories	No change	Improved by 1 or 2 categories	Total
	Deteriorated by 1 or 2 categories	23 (2.61%)	24 (2.73%)	5 (.57%)	52 (5.92%)
	No change	32 (3.64%)	193 (21.96%)	111 (12.63%)	336 (38.23%)
	Improved by 1 or 2 categories	4 (.46%)	95 (10.81%)	392 (44.60%)	491 (55.86%)
	Total	59 (6.72%)	312 (35.50%)	508 (57.80%)	879 (100.00%)

Table 13b: Number of Subjects by each Level of Response (in Pain/Discomfort Rating) to Elmiron at Three Months Versus the Reported Response at 9 Months

Change (from Baseline) in Pain/Discomfort Score at Nine Months					
Change (from Baseline) in Pain / Discomfort Score at Three Months		Deteriorated by 1 or 2 categories	No change	Improved by 1 or 2 categories	Total
	Deteriorated by 1 or 2 categories	8 (2.84%)	14 (2.21%)	5 (.79%)	37 (5.84%)
	No change	21 (3.32%)	123 (19.43%)	88 (13.90%)	232 (36.65%)
	Improved by 1 or 2 category	4 (.63%)	62 (9.79%)	298 (47.08%)	364 (57.50%)
	Total	43 (6.80%)	199 (31.44%)	391 (61.77%)	633 (100.00%)

Table 13c: Number of Subjects by each Level of Response (in Pain/Discomfort Rating) to Elmiron at Three Months Versus the Reported Response at 12 Months

Change (from Baseline) in Pain/Discomfort Score at Twelve Months					
Change (from Baseline) in Pain / Discomfort Score at Three Months		Deteriorated by 1 or 2 categories	No change	Improved by 1 or 2 categories	Total
	Deteriorated by 1 or 2 categories	5 (1.19%)	14 (3.34%)	4 (.95%)	23 (5.46%)
	No change	15 (3.57%)	97 (23.04%)	61 (14.49%)	173 (41.09%)
	Improved by 1 or 2 categories	2 (.49%)	36 (8.55%)	187 (44.42%)	225 (53.45%)
	Total	22 (5.24%)	147 (34.92%)	262 (59.85%)	421 (100.00%)

4.3 Reviewers' Conclusions Regarding Efficacy

- The data suggests that the IC population can be divided into "Elmiron responder" and "Elmiron non-responder" groups. Approximately 25% of IC patients appear to be "Elmiron responders" while 75% of IC patients seem to fall in the "Elmiron non-responder" group.
- Baseline nocturia ($p=0.028$) was the only parameter out of 13 which was even marginally statistically significant in predicting a patient's response or non-response to Elmiron. This result is not completely reliable however due to the exploratory data analysis and multiple comparison issues associated with the analysis used to identify this parameter.
- On average in the Elmiron responder group, patients' ratings of their overall change in IC, pain, and urgency fell between "moderately improved" and "greatly improved" ($p<0.001$). Elmiron responder patients' pain/discomfort and pressure to urinate ratings dropped on average approximately one category ($p<0.001$). On average, Elmiron responder subjects' urinary frequency decreased by four to five occurrences and their nocturia decreased by two occurrences ($p<0.001$).
- The reader should note however that the drug effect could be confounded with a placebo effect in these comparisons. The placebo effect may be the sole reason for the changes in the efficacy parameters or it may be merely

enhancing the drug effect and contributing to the magnitude of the observed effect.

- Once a patient is identified as a responder to Elmiron, the less severe that patient's baseline condition, the less dramatic the improvement. It is even possible that a slight deterioration in that patient's condition could occur. Again this trend may be criticized due to the exploratory and multiple comparisons procedures which were used to identify it.
- A three month "trial period" using Elmiron seems to be adequate to classify patients as an "Elmiron responder" or "Elmiron non-responder".

N.B. Medical Reviewer's Comment

To be complete, the highlights of the results of the second efficacy analysis of pivotal study 002 are presented:

- Elmiron demonstrated a significant difference from placebo in 2 of the 6 primary efficacy endpoints (after a Bonferroni correction). These endpoints were (1) investigator global evaluation of overall improvement, and (2) patient global evaluation of overall improvement in bladder pain.
- This study suffered from a serious treatment-by-investigator effect. The results were highly influenced by 1 investigator; when this investigator's data was excluded from the analysis, a trend in favor of Elmiron remained but the difference from placebo was no longer statistically significant (with a Bonferroni correction).
- This study was deemed to provide "supportive evidence for the applicant's efficacy claim" by Elizabeth A. Turney, M.S., Division of Biometrics in her review dated September 30, 1993.

5.0 MEDICAL REVIEWER'S OVERALL ASSESSMENT

- Interstitial cystitis is a multifactorial disease of unknown etiology that varies in clinical course from patient to patient. The pathophysiology has yet to be fully delineated. Multiple attempts to find a suitable treatment have been unsuccessful. The disease is non-fatal however the patient's quality of life is poor.
- This NDA for Elmiron attempts to provide a new treatment for patients with interstitial cystitis. Elmiron has been given an Orphan Drug designation.
- The pharmacokinetics and pharmacodynamics of Elmiron have not been fully delineated in this NDA.
- The data submitted in this NDA demonstrated a safety profile for Elmiron that is acceptable during the first 3 months of use particularly, but also after up to one year of use.
 - Nausea, diarrhea and alopecia were the most commonly found adverse drug reactions during the clinical development of this product. However, the incidence was small and the severity was minimal. Most importantly, the incidence of any severe toxicity was very low. This trend continued for up to 1 year of administration.
- To support the efficacy of Elmiron, the sponsor uses the results from 2 studies: pivotal study 002 and the Compassionate Use study. Each study, however, has multiple statistical concerns that ordinarily would be considered fatal flaws for an NDA.
 - The pivotal study demonstrated a statistically significant treatment effect in favor of Elmiron in 2 of the 6 endpoints (the patient's global evaluation of bladder pain, and the investigator's global evaluation of overall improvement). However, a significant treatment-by-investigator effect was present which adds doubt as to the validity of the results.
 - The Compassionate Use study data suggested an improvement from baseline with Elmiron use in all 7 efficacy endpoints. It is important to remember that this study was unblinded and uncontrolled and that the observed effect may be enhanced by a placebo effect. It is also very important to emphasize that only a subset of patients assumed to be "responders" were analyzed.
- The results of the Compassionate Use study suggest that a 3 month "trial period" using Elmiron seems to be adequate to identify a patient

as an "Elmiron responder" or "Elmiron non-responder."

- The results of a regression analysis suggest that baseline nocturia could possibly be used to predict who will respond favorably to Elmiron.
- The regulatory decision for this product is not clearcut. After considering the statistical and scientific facts, this NDA is not approvable. However, the clinical aspects of this NDA should also be taken into consideration. Given the natural history of interstitial cystitis, the low frequency of clinically significant toxicity with Elmiron use, and the suggestion of efficacy in at least a subset of patients, the medical risk/benefit ratio is acceptably small for this subset of patients.
- This reviewer's degree of comfort with the risk/benefit ratio, and hence my opinion, is contingent upon the sponsor upholding a previously stated commitment to accept an indication to treat for 3 months; if after 3 months no improvement is seen, then Elmiron will be discontinued.
- The sponsor's commitment to conducting Phase 4 investigations increases this reviewer's degree of comfort. A Phase 4 commitment will allow for the study of multiple questions that have not been answered in this NDA, and will provide more intense monitoring of safety and efficacy issues.

6.0 MEDICAL REVIEWER'S OVERALL RECOMMENDATION

- With a labeled indication that calls for the administration of Elmiron for 3 months with reassessment at that time and discontinuation if no effectiveness is seen, this NDA is approvable.
- Other requirements for the sponsor to meet prior to approval of the product:
 - submit draft labeling
 - submit a complete patient safety database for the Compassionate Use study
- The following should be submitted as soon as possible but not necessarily prior to a final decision:
 - perform a demographic subset analysis for safety and efficacy

(based on age, race, gender) for the pivotal and compassionate use databases

- submit a more detailed report of the pharmacokinetic study conducted by Jallad. Please include the raw data. If new studies have been performed, please submit the raw data and your analysis along with your conclusion.
 - validate the assay for intact PPS
 - study the effect of food on the bioavailability of Elmiron
 - study the pharmacokinetics of Elmiron in patients with liver disease
- commit to Phase 4 studies
 - to answer the above pharmacokinetic questions
 - continue to determine if there is a subset of "responders", and if so, identify a characteristic to predict who will respond
 - tease out gastrointestinal toxicity due to the drug versus that due to underlying diseases/disorders
 - continue to monitor long term adverse drug reactions

This reviewer's specific thoughts regarding the methodology that should be employed in the Phase 4 studies will follow as an addendum to this NDA review.

- devise a patient education sheet
- devise a patient adverse drug event monitor card

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Concur:

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cc IND ARCH
HFD-160/DIV FILES
HFD-160/DIVDIR
HFD-160/MEDGRPLEADER
HFD-160/PASERCHIA
HFD-344/A. LJSOOK
HFD-701/C. ANELLO
HFD-720/BIOMETRICS/N. SMITH
HFD-720/BIOMETRICS/R. DAVI
HFD-160/CSO
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7.0

APPENDIX A : Efficacy Tables**Table 1 : Distribution of Patients Across Baseline Conditions***

Demographic Factor	Baseline Condition of All Patients Entering the Compassionate Use Program	Baseline Condition of Patients Who Participated in the Compassionate Use Program for At Least Three Months	Baseline Condition of Patients Who Participated in the Compassionate Use Program for At Least One Year
Age (in years)			
x < 18	3 / 2443=0.12%	1 / 1169=0.09%	0 / 589=0.00%
18 ≤ x < 65	1974 / 2443=80.80%	947 / 1169=81.01%	493 / 589=83.70%
x ≥ 65	466 / 2443=19.07%	221 / 1169=18.90%	96 / 589=16.30%
Gender			
male	257 / 2477=10.40%	117 / 1185=9.87%	53 / 595=8.91%
female	2220 / 2477=89.60%	1068 / 1185=90.13%	542 / 595=91.09%

*Note: Sample size is varying across demographic factors due to missing data.

APPENDIX A : Efficacy Tables (Cont.)

Table 2 : Distribution of Patients Across Baseline Disease Status*

Baseline Disease Status	Baseline Disease Status of All Patients Entering the Compassionate Use Program	Baseline Disease Status of Patients Who Participated in the Compassionate Use Program for At Least Three Months	Baseline Disease Status of Patients Who Participated in the Compassionate Use Program for At Least One Year
Disease Duration (in years)			
0 to 1	136 / 2313=5.88%	71 / 1106=6.42%	31 / 555=5.60%
1 to 5	1138 / 2313=49.20%	528 / 1106=47.74%	284 / 555=51.17%
5 to 10	552 / 2313=23.87%	275 / 1106=24.86%	138 / 555=24.86%
10 or more	487 / 2313=21.05%	232 / 1106=20.98%	102 / 555=18.38%
Severity of Drainage (6 pt. scale)			
Rating = 0, None	383 / 2310=16.58%	185 / 1095=16.89%	92 / 545=16.88%
Rating = 1, Limited	299 / 2310=12.94%	147 / 1095=13.42%	72 / 545=13.21%
Rating = 2, ...	344 / 2310=14.89%	163 / 1095=14.86%	82 / 545=15.05%
Rating = 3, ...	409 / 2310=17.71%	261 / 1095=23.84%	129 / 545=23.67%
Rating = 4, ...	493 / 2310=21.34%	230 / 1095=21.00%	120 / 545=22.02%
Rating = 5, Extensive	242 / 2310=10.48%	109 / 1095=9.95%	50 / 545=9.17%
Fissures (6 pt. scale)			
Rating = 0, None	353 / 2310=15.28%	180 / 1111=16.20%	85 / 555=15.32%
Rating = 1, Limited	225 / 2310=9.74%	106 / 1111=9.54%	52 / 555=9.37%
Rating = 2, ...	284 / 2310=12.29%	117 / 1111=10.53%	62 / 555=11.17%
Rating = 3, ...	609 / 2310=26.36%	298 / 1111=26.82%	158 / 555=28.47%
Rating = 4, ...	612 / 2310=26.49%	289 / 1111=26.01%	142 / 555=25.59%
Rating = 5, Extensive	259 / 2310=11.21%	121 / 1111=10.89%	56 / 555=10.09%
Petechial Hemorrhages (6 pt. scale)			
Rating = 0, None	164 / 2342=7.00%	88 / 1109=7.94%	39 / 554=7.04%
Rating = 1, Limited	170 / 2342=7.26%	72 / 1109=6.49%	31 / 554=5.60%
Rating = 2, ...	268 / 2342=11.44%	122 / 1109=11.00%	65 / 554=11.73%
Rating = 3, ...	609 / 2342=26.00%	308 / 1109=27.77%	156 / 554=28.16%
Rating = 4, ...	749 / 2342=31.98%	329 / 1109=29.67%	173 / 554=31.23%
Rating = 5, Extensive	382 / 2342=16.31%	190 / 1109=17.13%	90 / 554=16.25%
Hunner's Ulcers			
Present	347 / 2375=14.61%	188 / 1124=16.73%	95 / 563=16.87%
Not Present	2028 / 2375=85.39%	936 / 1124=83.27%	468 / 563=83.13%
Baseline Pain/Discomfort Score (3 pt. scale)			
None/Mild	170 / 2352=7.23%	77 / 1127=6.83%	38 / 569=6.68%
Moderate	781 / 2352=33.21%	395 / 1127=35.05%	214 / 569=37.61%
Severe/Unbearable	1401 / 2352=59.57%	655 / 1127=58.12%	317 / 569=55.71%
Baseline Urgency (4 pt. scale)			
None	108 / 2467=4.38%	45 / 1174=3.83%	21 / 586=3.58%
Mild	229 / 2467=9.28%	116 / 1174=9.88%	52 / 586=8.87%
Moderate	862 / 2467=34.94%	406 / 1174=34.58%	219 / 586=37.37%
Severe	1268 / 2467=51.40%	607 / 1174=51.70%	294 / 586=50.17%
Baseline Frequency (#occurrences)			
$x < 20$	1514 / 2413=62.74%	760 / 1153=65.92%	402 / 577=69.67%
$20 \leq x < 50$	801 / 2413=33.20%	350 / 1153=30.36%	156 / 577=27.04%
$x \geq 50$	98 / 2413=4.06%	43 / 1153=3.73%	19 / 577=3.29%

Baseline Nocturia (#occurrences)

x = 0	1245 / 2418=51.49%	605 / 1156=52.34%	314 / 577=54.42%
5 ≤ x < 20	1094 / 2418=45.24%	521 / 1156=45.07%	250 / 577=43.33%
x ≥ 20	79 / 2418=3.27%	30 / 1156=2.60%	13 / 577=2.25%

*Note: Sample size is varying across baseline disease status due to missing data.

APPENDIX A : Efficacy Tables (Cont.)

Table 3 : Change in Efficacy Parameters Stratified by Baseline Characteristics

Efficacy Parameter	Baseline Score	At least One Year of Participation	At least Two Years of Participation	At least Three Years of Participation
Pain / Discomfort Score ¹ (Baseline - Final Measurement)	none/mild	N=36, Median = 0.0 Mean= -0.42 CI: (-0.80, -0.23)	N=12, Median = 0.0 Mean= -0.25 CI: (-0.54, 0.04)	N=4, Median = 0.0 Mean= 0 CI: (0, 0)
	moderate	N=183, Median = 1.0 Mean= 0.48 CI: (0.38, 0.57)	N=101, Median = 1.0 Mean= 0.57 CI: (0.45, 0.69)	N=49, Median = 1.0 Mean= 0.61 CI: (0.45, 0.78)
	severe / unbearable	N=281, Median = 1.0 Mean= 1.16 CI: (1.07, 1.25)	N=139, Median = 1.0 Mean= 1.27 CI: (1.15, 1.39)	N=73, Median = 1.0 Mean= 1.36 CI: (1.19, 1.52)
Pressure to Urinate ² (Urgency) (Baseline - Final Measurement)	none	N=19, Median = -1.0 Mean= -1.21 CI: (-1.73, -0.69)	N=8, Median = -1.0 Mean= -1.13 CI: (-2.07, -0.18)	N=2, Median = -1.0 Mean= -1.00 CI: Indeterminant
	mild	N=15, Median = 0.0 Mean= -0.06 CI: (-0.29, 0.17)	N=22, Median = 0.0 Mean= 0.05 CI: (-0.33, 0.42)	N=7, Median = 0.0 Mean= 0.143 CI: (-0.50, 0.78)
	moderate	N=183, Median = 1.0 Mean= 0.69 CI: (0.57, 0.81)	N=96, Median = 1.0 Mean= 0.76 CI: (0.60, 0.92)	N=47, Median = 1.0 Mean= 0.70 CI: (0.47, 0.93)
	severe	N=267, Median = 1.0 Mean= 1.33 CI: (1.22, 1.44)	N=132, Median = 2.0 Mean= 1.53 CI: (1.39, 1.67)	N=69, Median = 2.0 Mean= 1.65 CI: (1.47, 1.84)
Frequency of Urination ³ (Baseline - Final Measurement)	baseline ≤ 7/day	N=47, Median = -1.0 Mean= -1.79 CI: (-2.80, -0.77)	N=21, Median = -1.0 Mean= -1.43 CI: (-2.84, -0.02)	N=7, Median = -4.0 Mean= -2.43 CI: (-5.09, 0.23)
	8/day ≤ baseline ≤ 24/day	N=371, Median = 3.0 Mean= 2.10 CI: (0.95, 3.25)	N=188, Median = 2.5 Mean= 1.76 CI: (-0.30, 3.82)	N=99, Median = 3.0 Mean= 3.13 CI: (1.60, 4.67)
	25/day ≤ baseline ≤ 72/day	N=81, Median = 16 Mean= 17.23 CI: (13.13, 21.33)	N=38, Median = 16.5 Mean= 16.74 CI: (9.95, 23.52)	N=16, Median = 19.0 Mean= 18.19 CI: (9.48, 26.89)
Frequency of Nocturia ³ (Baseline - Final Measurement)	baseline ≤ 2/night	N=110, Median = 0.0 Mean= -0.03 CI: (-0.22, 0.17)	N=47, Median = 0.0 Mean= -0.19 CI: (-0.51, 0.13)	N=20, Median = 0.0 Mean= -0.20 CI: (-0.80, 0.40)
	3/night ≤ baseline ≤ 10/night	N=357, Median = 2.0 Mean= 1.64 CI: (1.51, 2.16)	N=186, Median = 2.0 Mean= 2.00 CI: (1.52, 2.47)	N=97, Median = 3.0 Mean= 2.89 CI: (2.35, 3.43)
	11/night ≤ baseline ≤ 24/night	N=36, Median = 8.0 Mean= 6.67 CI: (3.25, 10.08)	N=18, Median = 8.5 Mean= 5.67 CI: (-0.75, 12.08)	N=7, Median = 7.0 Mean= 5.14 CI: (-5.22, 15.51)

1. Measured on a 10 point scale. Collapsed at the request of FDA to a three point scale: 1=none or mild, 2=moderate, 3=severe or unbearable,
 2. Measured on a four point scale: 1=none, 2=mild, 3=moderate, 4=severe
 3. Subject's estimated number per day (night)

8.0 APPENDIX B: Adverse Drug Reactions Grouped by Body System

ADR	Patients (n = 2506)		Maximum Severity				Related to Elmiron?			Elmiron Continued?		
	#	%	Mild	Mod	Sev	Unk	Yes	No	Unk	Yes	No	Unk
Gastrointestinal												
diarrhea		3.9	19	18	8	53	67	8	23	47	44	7
nausea		3.7	12	17	11	53	60	11	22	40	47	6
dyspepsia		2.2	8	11	5	31	27	9	19	20	30	5
abdominal pain		2.0	6	9	1	32	22	9	20	16	30	5
SGOT elevated		0.28	0	1	0	6	1	2	4	3	4	0
SGPT elevated		0.24	1	2	0	3	4	1	1	1	5	0
LFT abnormality		1	6	4	0	16	17	1	8	10	15	1
Hemalogic												
ecchymosis		0.72	8	2	0	8	11	3	4	6	11	1
thrombocytopenia		0.24	1	0	0	5	0	0	6	2	4	0
Urogenital												
hematuria		0.52	2	3	0	8	4	5	4	6	7	0
Pulmonary												
epistaxis		0.32	2	0	1	5	5	0	3	1	7	0
Body as a Whole												
allergic reaction		0.24	1	1	0	3	3	2	0	2	3	0
face edema		0.12	1	0	0	2	2	0	1	1	2	0
generalized edema		0.04	0	0	0	1	0	0	1	0	1	0
death		0.12	0	0	1	2	0	3	0	0	3	0
Skin												
alopecia		3.9	17	21	3	57	60	9	29	44	52	2
rash		2.6	8	6	4	46	34	11	19	27	35	2
Neurologic												
headache		2.8	6	17	5	42	40	15	15	34	35	1
dizziness		1.1	0	6	3	19	20	3	5	10	17	1
asthenia		1.1	3	5	2	17	14	4	9	16	10	1

APPENDIX C: Additional Tables

Table 1: NDA 20,193 - Elmiron
NDA Database - Patient Enrollment/Discontinuation

N	Study E001		Study E002		Compassionate Use Program	Total	
	Elmiron	Placebo	Elmiron	Placebo	Elmiron	Elmiron	Placebo
Entered	54	56	76	75	2499	2629	131
Exposed to Elmiron	54	56	74	74	2499	2627	130
Completed	51	47	65	65	1192 ¹	1308	112
Drop-ADR	1	2	3	5	218 ²	222	7
Drop-Failed to Return	0	0	6	4	71 ²	77	4
Drop-Death	0	0	0	0	0 ²	0	0
Drop-Lack of Efficacy	0	1	0	0	344 ²	344	1
Drop-Other	0	0	0	0	407 ²	407	0
Drop-Investigator did not provide explanation	2	6	0	0	NA ³	2	6

1. Number of subjects who completed at least *three months* of Elmiron use during the compassionate use program.
2. Number of subjects who discontinued by *three months* during the compassionate use program.
3. For the compassionate use submission, the sponsor incorporated missing explanations into the "other" category.

Table 2: NDA 20,193 - Elmiron
NDA Database - #ADR's

Study Number	Type of Study	# Subjects (Placebo)	# Subjects (Elmiron)	# ADR's (Placebo)	#ADR's (Elmiron)
E001	Phase 3	56	54	9	9
E002	Phase 3	74	74	19	12
Compassionate Use Program	Open-label Uncontrolled	NA	2504	NA	1146 ¹
Total	NA	130	2632	28	1167

1. Number of ADR's which occurred within 12 months of Elmiron use during the compassionate use program.

Appendix D

5.

APPENDIX D
SAFETY REPORTS FILED WITH THE FDA

Daily Dose	Duration of Exposure to Drug	Adverse Event/Summary	Investigator Assigned Relationship to Elmiron®
100 mg TID	10/1/87 to 12/1/87	Renal Failure: A 59 year old white female started Elmiron® therapy in October 1987. Subsequent to the initial Elmiron® treatment, the patient who had a previous history of mild to moderate renal failure experienced slow progression of her disease. The treating physician was unaware of the patient's medical history prior to treating the patient with Elmiron®. Elmiron® treatment was discontinued.	Unrelated
100 mg TID	2/88 to 7/91	Leukemia: A 46 year old white female with a family history of a "fatal blood disease" received Elmiron® (300 mg/day) for 3 years. Routine review of the patient's laboratory results by Baker Norton Medical Department prior to the fulfillment of the patient's drug reorder request indicated significant leukocytosis (25,000 x 10 ³ CU.MM) and the presence of metamyelocytes in her differential count. All previous counts had been normal. Subsequent evaluation results for the patient (bone marrow aspiration, biopsy and chromosome studies) were positive for a myeloproliferative disorder such as chronic granulocytic leukemia. Elmiron® was discontinued. There were no prior reports of leukemia in any patient on Elmiron® therapy.	Unrelated
100 mg TID	8/6/91 to 11/4/91	Aneurysm: A 48 year old white female who was diagnosed with interstitial cystitis and had been taking Elmiron® (300 mg/day) for 9 weeks, noticed a severe headache associated with temporary loss of consciousness prior to being involved in an auto accident. There was no history of hypertension, cerebrovascular events or coagulopathy. On admission to an emergency room she was evaluated and her spinal tap, CT and arteriogram were positive for a subarachnoid bleed. No aneurysm was initially seen on her arteriogram and her coagulation profile was normal. Hemoglobin and hematocrit were in the normal range. Repeat angiograms revealed a ruptured anterior cerebral artery aneurysm. A right frontal craniotomy was performed and the aneurysm was clipped. The patient was discharged in stable condition with no reported neurologic deficit. Elmiron® therapy was discontinued during the patient's hospitalization.	Unrelated
100 mg TID	3/91 to 11/91	Death in a previously diagnosed metastatic malignant melanoma patient: A 55 year old white male diagnosed with interstitial cystitis, was placed on Elmiron®. In February 1992 the patient died as a result of metastatic malignant melanoma which had been diagnosed prior to Elmiron® therapy initiation. The attending physician in response to Baker Norton Medical Department's follow-up inquiries indicated that the patient's death was not considered to be Elmiron® related as the patient had discontinued taking Elmiron® several months before his death and the melanoma was diagnosed prior to Elmiron® therapy.	Unrelated

APPENDIX F
SAFETY REPORTS FILED WITH THE FDA

Daily Dose	Duration of Exposure to Drug	Adverse Event/Summary	Investigator Assigned Relationship to Elmiron®
100 mg TID	3/18/92 to 6/10/92	Anterior Myocardial Infarction: A 61 year old white hypertensive male with hypertriglyceridemia, "thyroid disease" and a prior history of scarlet fever was taking Elmiron® for 3 months prior to hospitalization. His concomitant medications were Hytrin, thyroid extract and Ativan. During his hospitalization he was diagnosed as having anterior myocardial infarction. He suffered no sequelae. Elmiron® therapy was discontinued.	Unrelated
100 mg TID	4/88 to 6/92	Prostatic Carcinoma: A 62 year old white male was hospitalized for a routine transurethral resection of the prostate (TURP) for benign prostatic hypertrophy (BPH). One resected fragment was found to have a focus of carcinoma. The results supported a diagnosis of stage A-1 carcinoma. The patient's bone scan was negative. Prior to his hospitalization, the patient had been responding to Elmiron® with improvement of his IC symptoms for four years. The patient subsequently continued his Elmiron treatment®.	Unrelated
100 mg TID	4/92 to Unknown	Death/Stroke: A 72 year old hypertensive, arteriosclerotic, hypercholesterolemic, white male with thyroid disease commenced Elmiron® therapy on April 2, 1992. During 1992 the patient died of a stroke. Concomitant medications were Synthroid, Tenormin, Mevacor, oxybutynin, Prinivil, verapamil, Levsinex, Bactrim, amitriptyline. A review of the patient's February 1992 laboratory results indicated an elevated serum glucose of 147 mg/dl, normal PT (11.7 seconds) and normal APTT (31 seconds) with an adequate platelet count.	Unknown
100 mg TID	10/91 to 8/92	Peptic Gastric Ulcer: A 32 year old female on Elmiron® therapy for 10 months complained of abdominal pain. She was later diagnosed as having a peptic gastric ulcer. Concomitant medications were Orudis, Decadron, Anaprox, Prednisone, Meclizine, and Motrin. These medications and Elmiron® were discontinued and the patient's condition improved.	Related
100 mg TID	2/92 to 11/92	Optic Neuritis: A 42 year old white female was noted to have a left unilateral central optic scotoma in November 1992. Ophthalmologic and neurologic examinations were negative for multiple sclerosis. The patient was diagnosed as having left optic neuritis. There was no history of excessive alcohol intake, sinusitis, diabetes, vitamin deficiency, hypertension, lupus erythematosus or previous visual problems. Her ophthalmological condition stabilized and she was continued on Elmiron® therapy.	Remote
100 mg TID	4/88 to 1/2/93	Acute Inferior Wall Myocardial Infarction: A 59 year old female was diagnosed as having hypercholesterolemia. The patient was hospitalized on 1/2/93 and underwent a cardiac bypass on 1/3/93. Elmiron® was discontinued prior to surgery. Post-operative complications were aspiration pneumonia, sepsis, deep lower limb vein thrombosis and cerebral infarction. The patient died on 2/12/93; 1 1/2 months following the surgery.	Unrelated

APPENDIX F
SAFETY REPORTS FILED WITH THE FDA

Daily Dose	Duration of Exposure to Drug	Adverse Event Summary	Investigator Assigned Relationship to Elmiron®
100 mg TID	9/91 to 2/10/93	Bilateral Retinopathy: A 65 year old white hypertensive diabetic female had a ophthalmological history of seeing "black spots" for over 5 years prior to taking Elmiron®. While on Elmiron® the patient was diagnosed as having bilateral retinopathy. Concomitant medications were Elavil, Cardizem and Lozol. Elmiron® was discontinued.	Unrelated
100 mg TID	6/89 to 2/24/93	Heart Palpitations and Elevated Blood Pressure: A 32 year old white female without prior history of hypertension, thyroid disease, kidney disease, increased caffeine intake or cardiac arrhythmias experienced heart palpitations and elevated blood pressure while on Elmiron®. Evaluation of the patient's Holter monitor revealed ventricular ectopy with several premature ventricular contractions (PVCs). The patient did not complain of angina and did not require hospitalization. Premarin was being taken concomitantly. Elmiron® was discontinued on 2/24/93.	Unrelated
100 mg TID	11/92 to 3/19/93	Blurred Vision, Left Central Optic Vein Occlusion: A 32 year old white female without a prior history of eye trauma, hypertension, diabetes or previous significant ophthalmologic history complained of experiencing blurred vision. The patient had a negative cranial MRI and her platelet count and PTT were both normal. She was hypercholesterolemic. The patient had been taking Ovcon 28 (birth control pill) for several years. All medications including Elmiron® were stopped. The treating physician indicated that the prognosis for the patient's recovery was uncertain. He believed that the oral contraceptive was most likely the cause of the retinal vein occlusion.	Possible
100 mg TID	3/10/93 to 5/6/93	"Filmy Sensation Over Left Eye" Possible Left Optic Neuritis: A 21 year old white female without any history of ophthalmological problems, head trauma, diabetes or any previous neurological symptoms experienced a "filmy sensation over the left eye." An ophthalmological examination subsequent to the occurrence of this adverse event indicated decreased vision in the left eye. Concomitant medications were Percocet, Benadryl, Orudis, Lovral, Phenergan, Librax, Levinox, Zoloft and Vicodin. Product labeling for Orudis and Zoloft describe visual disturbances and visual abnormalities. The patient did not require hospitalization and there was no progression of her ophthalmologic condition. Elmiron® was discontinued on 5-6-93.	Unrelated
100 mg TID	10/91 to 7/30/93	Cushing's Syndrome: A 41 year old white female on Elmiron® therapy visited her treating physician for routine follow-up and was noted to have had a 2-month history of fatigue, dizziness, carbohydrate craving, moonlike facies and a 10 lb. weight gain over one month. She was also receiving monthly bladder installations of DMSO, heparin, Kenalog (steroid) and sodium bicarbonate. Concomitant medications were Prozac, Pamelor, Zoloft and Trazadone. The treating physician determined that the patient developed Cushing's Syndrome from the absorption of Kenalog during the frequent bladder installations. Elmiron® was discontinued on 7/30/93. The treating physician indicated that the patient was expected to fully recover from the Kenalog induced Cushing's Syndrome.	Unrelated

APPENDIX F
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Date/Dose	Duration of Exposure to Drug	Adverse Event/Summary	Investigator Assigned Relationship to Elmiron®
100 mg TID	1/18/91 to 7/7/93	Death-Metastatic Adenocarcinoma: A 75 year old hypertensive white female on Elmiron® therapy since 1/18/91 died on 1/18/93 from metastatic adenocarcinoma. The patient was seen by her treating physician with a 1 month history of intermittent abdominal pain localized to the epigastrium and was treated with Zantac. There was no history of weight loss, melena, hemoptysis or anemia. A CT scan of the abdomen showed "an inflammatory process involving the colon". A Gastrografin enema resulted in a diagnosis of diverticulosis and compression of the proximal sigmoid colon, secondary to a pericolic inflammatory mass. An exploratory laparotomy was performed and extensive abdominal peritoneal carcinomatosis was found. Biopsy of the omentum and small bowel mesenteric nodes confirmed metastatic poorly differentiated adenocarcinoma of unknown primary. The patient was discharged and later died at home. No autopsy was performed.	Remote
100 mg TID	5/93 to 8/93	Diarrhea & Dehydration: A 34 year old white female being treated with Elmiron® was hospitalized for 5 days for an evaluation and treatment of severe diarrhea (4-6 watery bowel movements per day) and dehydration. The patient had no history of recent travel outside of the United States, abdominal pain, vomiting, melena, inflammatory bowel disease, irritable bowel syndrome, steatorrhea, lactose intolerance, overuse of laxatives or prior gastric surgery. Her concomitant medications at the time of her hospitalization were imipramine hydrochloride, Motrin and Percocet. Complete G.I. evaluation was negative. She did not have anemia or electrolyte imbalance. With parenteral and dietary support, the diarrhea spontaneously remitted, and she was discharged and was asymptomatic and without sequelae. The patient was not rechallenged with Elmiron®.	Possible
100 mg TID	5/29/93 to 9/28/93	Thrombocytopenia: A 65 year old white female with a history of hypothyroidism, hypertension, depression, anxiety, hypercholesterolemia and chronic cephalgia had a reported platelet count of 67,000/mm³ on 9/28/93 and 65,000/mm³ on 10/6/93. Manual review of the same blood smears for 9/28/93 and 10/6/93 indicated platelet counts of 280,000/mm³ and 270,000/mm³, respectively. On 10/8/93 the platelet count was 238,000/mm³. The consulting hematologist determined that the previously reported low platelet counts were spurious and were solely due to machine error.	Unrelated
100 mg TID	5/12/93 to 10/29/93	Bilateral lower extremity edema and dyspnea: A 72 year old white hypertensive female was hospitalized on 10/29/93 for medical monitoring and diuretic therapy after suffering several episodes of dyspnea the previous week. The patient had a chronic history of hypertension, hypothyroidism, bilateral breast carcinoma, rheumatoid arthritis and recurrent urinary tract infection. The patient's concomitant medications were Maxzide, Synthroid, Megace (known to cause fluid retention) and Ditropan. All medications including Elmiron® were discontinued upon hospitalization. The patient was discharged 3 days after her hospital admission without sequelae.	Unrelated

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Daily Dose	Duration of Exposure to Drug	Adverse Event/Summary	Investigator Assigned Relationship to Elmiron®
100 mg TID	9/17/93 to 12/16/93	Death: A 74 year old obese, hypertensive white female whose Elmiron® therapy was discontinued in preparation for elective surgery (2 1/2 months prior to her death) died 4 weeks after gastroplasty and hiatal hernia repair. An autopsy was not performed. The patient had a chronic history of lower extremity deep vein thrombosis, reflux esophagitis, osteoarthritis, exogenous obesity, depression, and hypercholesterolemia. Post-operative complications were calf tenderness, pain, swelling and a positive Homan's sign; she was placed on parenteral heparin therapy. The patient was discharged 3 weeks following surgery and was placed on Coumadin therapy. Elmiron® was not reintroduced.	Unrelated
100 mg TID	4/93 to 7/2/94	Gastritis: A 65 year old hypothyroid, hypertensive, osteoarthritic, white female was hospitalized for evaluation of abdominal distention, epigastric pain, dyspepsia, anorexia, occult blood in the stool, diarrhea and constipation. Concomitant medications were Naprosyn, aspirin, Elavil, Zoloft, Synthroid, Norvaco, Bumex and Vasotec. Sigmoidoscopy and gastroscopy indicated internal hemorrhoids and superficial gastritis respectively. Her coagulogram and liver function tests were normal. The patient's symptoms resolved with treatment. The treating gastroenterologist indicated that the symptoms probably occurred as a result of the patient's use of nonsteroidal anti-inflammatory drugs. The patient was subsequently discharged without sequelae and remained on Elmiron®.	Remote
100 mg TID	1987 to 4/94	Death-Metastatic Bronchogenic Carcinoma: A 68 year old hypertensive white female with a chronic history of "heavy" cigarette smoking died from metastatic bronchogenic carcinoma. In 1/94 the patient presented with chest pain, weakness, dehydration, weight loss and was evaluated with the presumptive diagnosis of pneumonia. Chest X-ray and computerized tomography revealed a left upper lung mass contiguous with the mediastinum. Percutaneous fine needle biopsy was positive for adenocarcinoma. Her coagulogram was normal. The patient received combination chemotherapy (Platinol and Velban) and was subsequently hospitalized for treatment of severe nausea and dehydration secondary to chemotherapy. There were no hemorrhagic complications. Radionuclide scan was positive for bone metastases.	Unrelated
100 mg TID	2/8/94 to 5/94	Abdominal Pain: A 81 year old hypercholesterolemic female was hospitalized due to a history of abdominal pain which had increased in severity with sporadic episodes of diarrhea not associated with vomiting or melena. Concomitant medications were: Desyrel, Paxil, Librax, Klonopin, Mevacor, Premarin, Provera, Lomotil, Vicodin and Doxepin HCl. The patient was diagnosed as having cholelithiasis and was later discharged asymptomatic from the hospital.	Unrelated

APPENDIX F
SAFETY REPORTS FILED WITH THE FDA

Daily Dose	Duration of Exposure to Drug	Adverse Event/Summary	Investigator Assigned Relationship to Elmiron®
100 mg TID	5/89 to 1/94	Myocardial Infarction: A 68 year old white male whose Elmiron® had been discontinued for administrative reasons 5 months prior to an onset of substernal chest pain, diaphoresis and weakness was evaluated and found to have an acute anterolateral myocardial infarction. The patient had a history of coronary artery disease, episodes of paroxysmal atrial tachycardia, chronic atrial fibrillation, type II diabetes mellitus and myocardial infarction in 1966 prior to Elmiron® therapy. Concomitant medications were Lanoxin, Glyburide, Motrin and aspirin. ECGs revealed atrial fibrillation and evidence of progressive resolution of a anterolateral myocardial infarction. The patient was treated with IV streptokinase and heparin and was subsequently discharged from the hospital without sequelae.	Unrelated
Placebo or 200 mg TID	2/23/93 to 5/19/93	Weakness, Confusion and Death: An 80 year old white female with a history of hypertension and arthritis was hospitalized on 6/16/93 for evaluation and treatment of progressive weakness and confusion. She has a prior history of thyroid carcinoma. A liver ultrasound confirmed a diagnosis of metastatic carcinoma. The patient's clinical condition gradually deteriorated and she died on 7/10/93. Elmiron® therapy was discontinued on 5/19/93.	Unrelated
100 mg TID	12/93 to Present	Arteriosclerotic cardiovascular disease: The patient is a 67 year old white male with a history of arteriosclerotic cardiovascular disease, hyperlipidemia, angina pectoris, essential hypertension and a prior history of a cerebrovascular accident. Cardiac catheterization in 1990 revealed some degree of arteriosclerotic coronary artery disease. A subsequent cardiac catheterization (1994) revealed disease in 4 vessels and a coronary bypass was done. Patient received a pacemaker implant after developing "sick sinus syndrome". Elmiron® treatment was maintained throughout the patient's hospitalization and is presently being continued.	Unrelated
Placebo or 200 mg TID	4/29/93 to 7/21/93	Hemoptysis: A 58 year old white female with a prior chronic history of bronchiectasis experienced chills, fever and a "sore throat" 3 weeks prior to an episode of hemoptysis. Patient had previously experienced these symptoms prior to Elmiron® exposure and had undergone a left lobectomy 30 years prior for bronchiectasis. Patient was hospitalized and diagnosed as having hemoptysis due to bronchiectasis. Elmiron® treatment was discontinued.	Unrelated
100 mg	8/6/91 to 8/26/94	Liver Cancer: A 76 year old white male with a prior history of laryngeal carcinoma, alcohol abuse, cirrhosis, extensive radiation therapy was hospitalized on 8/26/94 for evaluation and treatment of symptoms consistent with cholecystitis. Patient had been previously hospitalized in 1981 for gastrointestinal hemorrhage caused by excessive alcohol intake. At exploratory laparotomy and cholecystectomy, he was noted to have a liver mass which was biopsied. The results from the biopsy indicated grade I primary liver carcinoma; a metastatic evaluation was negative. Elmiron® therapy was discontinued.	Unknown

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SAFETY REPORTS FILED WITH THE FDA

Daily Dose	Duration of Exposure to Drug	Adverse Event/Summary	Investigator Assigned Relationship to Elmiron®
Placebo or 200 mg TID	8/3/94 to 10/2/94	Hemiplegia: A 73 year old female with a history of chronic atrial fibrillation, essential hypertension and history of myocardial infarction developed left side weakness on 10/3/94 and was hospitalized for evaluation of sudden onset of left hemiplegia. At admission, clotting parameters, blood urea, electrolytes, CBC and chest x-ray were normal. Study drug was discontinued on 10/2/94. Due to the severity of the patient's condition, the study code was broken and the patient was found to have been a placebo.	Unrelated
200 mg TID	Unknown	Tooth Abscess: A 48 year old white female was hospitalized on 9/9/94 for drainage of a tooth abscess. While hospitalized she received intravenous antibiotic therapy, oral diclofenac sodium, intravenous metronidazole. Intravenous cephadrine followed by oral metronidazole and cephadrine. The patient was discharged 3 days after admission without sequelae and resumed Elmiron® treatment.	Unrelated
100 mg TID	2/17/94 to 11/3/94	Breast Cancer: A 38 year old white female with a history of mitral prolapse and low plasma thyroxin was found to have a nodule in the right breast in October 1994. There was no family history for breast cancer. Her biopsy was positive for infiltrating intraductal carcinoma. Axillary lymph nodes were negative for tumor. The patient underwent a "lumpectomy" and was scheduled for follow-up chemotherapy. Elmiron® was discontinued.	Unrelated
200 mg TID	6/28/94 to 12/2/94	Urinary Retention: A 73 year old hypertensive white male with a history of urinary hesitancy and "prostatism" secondary to benign prostatic hypertrophy was discontinued from Elmiron® on 12/2/94 in preparation for cystoscopy. Post cystoscopy, on 12/12/94 the patient was hospitalized, evaluated and treated for acute urinary retention. The treating physician related that the urinary retention was due to benign prostatic hypertrophy.	Unrelated
100 mg TID	9/93 to 1/94	Congestive Heart Failure: A 79 year old white female with a past history of hypothyroidism, Paget's disease of the bone, stenosis of the small bowel (duodenal web), status post hysterectomy and gastric reaction died in July 1994, 6 months after discontinuing Elmiron®. Concomitant illnesses were dehydration, malnutrition, hypothyroidism and diarrhea. While on Elmiron® therapy, the patient did not report signs of symptoms of cardiac disease, edema, dyspnea, abnormal renal function, hemoptysis or cyanosis. Approximately 3 months prior to her death the patient underwent an augmentation cystoplasty.	Unrelated

Appendix D

6.

APPENDIX F
SAFETY REPORTS FILED WITH THE FDA

Daily Dose	Duration of Exposure to Drug	Adverse Event/Summary	Investigator Assigned Relationship to Elmiron®
100 mg TID	2/91 to 2/93	Myocardial Infarction: A 51 year old hypertensive obese male suffered an myocardial infarction 2/93. He had a strong family history of coronary artery disease; his brother suffered a myocardial infarction and died at age 65 and his mother underwent coronary artery bypass graft surgery (CABG). The patient has smoked 4 cigars per day for the past 30 years and claimed to be under job-related stress. Subsequent to his myocardial infarction he successfully underwent coronary bypass surgery for severe multivessel disease. Elmiron® was discontinued on admission.	Unknown
100 mg TID	6/1/94 to 9/94	Heart Attack: A 54 year old female with a history of coronary artery disease, insulin dependant diabetes mellitus and hypertension reported to her urologist that she suffered a "heart attack" in November 1994 approximately 2 months after Elmiron® therapy was discontinued.	Unrelated
200 mg TID	3/15/95 to Present	Urinary Retention: One month after receiving Elmiron® a 71 year old female experienced an episode of acute urinary retention which required overnight hospitalization. There was no history of neurogenic bladder. Previous to receiving open-label Elmiron®, the patient was enrolled in the double-blind, placebo-controlled study with Elmiron®. The treatment blind was not broken. The patient was discharged voiding well without sequelae and resumed Elmiron® therapy.	Possible

NDA20193

11.0 REFERENCES

1. Erickson DR, Lecture presented at George Washington University Urology Grand Rounds on November 8, 1995 entitled: Interstitial Cystitis: Research Advances and Clinical Pearls.
2. Jean Fourcroy, MD, Division of Endocrine and Metabolism, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, personal communication.
3. Losonczy H, et. al.: Effect of Pentosan Polysulfate on Activated Partial Thromboplastin Time, Thrombin Time, Euglobulin Clot Lysis, and on Tissue-Type Plasminogen Activator and Plasminogen Activator Inhibitor Activities in Patients with Thromboembolic Disease. Sem Thromb and Hemost 17(4), 394;1991.
4. Koziol, JA: Epidemiology of Interstitial Cystitis. The Urologic Clinics of North America: Interstitial Cystitis 21(1), 7;1994.

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PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-193 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 160 Trade and generic names/dosage form: Flavirin (penicillin polyethylene ester) Action AP AE NA

Applicant Baker-Nelson Pharmaceuticals Therapeutic Class S

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate _____ inadequate _____

Indication in this application Relief of pain or discomfort associated with interstitial cystitis (For supplement answer the following questions in relation to the proposed indication.)

- 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing.
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Sharon Crockett
Signature of Preparer and Title

Sept 20 1996
Date

cc: Orig NDA/PLA/PMA # 20-193
HFD 160 /Div File
NDA/PLA Action Package
HFD-006/ SO instead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

**DIVISION OF MEDICAL IMAGING AND
RADIOPHARMACEUTICAL DRUG PRODUCTS**

PEDIATRIC PAGE MEMO

Elmiron (pentosan polysulfate sodium) is indicated for the relief of pain or discomfort associated with interstitial cystitis. Interstitial cystitis primarily affects adult women. Therefore, Elmiron has no pediatric indications at this time, nor does the sponsor intend to pursue any.

This application was submitted 6-11-91

No Debarment Certification is Needed.

NDA: 20-195
DRUG: Elmiron (pentosan polysulfate sodium) capsules
INDICATION: Interstitial Cystitis
CATEGORY: Response to Approvable Action
STATUS: Orphan
SPONSOR: Baker Norton Pharmaceuticals, Inc.
SUBMITTED: April 10, 1996
COMPLETED: September 23, 1996

DIVISION DIRECTOR BRIEF COMMENT

Elimiron (pentosan polysulfate sodium) capsules for oral administration in the treatment of Interstitial Cystitis was approvable as of March 1, 1996. (Effective August, 1985, Elmiron has Orphan designation for this indication). In the approvable letter, the sponsor was requested to revise the labeling, submit additional safety data, and submit a pharmacokinetics raw data and assay validation. As comprehensively covered in the Deputy Director Memorandum to the File (that serves as the primary and team leader reviews), with one exception, the sponsor has adequately responded to the requests in the approvable letter. The one exception is Biopharmaceutics. The resubmission states that these data were not available to the sponsor. After discussions of the issues with the reviewer and Dr. Raczkowski, it was determined that new studies can be completed in phase 4. A commitment to do so is contained in the resubmission.

After reviewing Dr. Raczkowski's comments, I agree with his overall assessments. Administratively, the other point is whether revised labeling and revised promotional campaign must be reviewed before approval, (noted at the end of the Deputy Memorandum). This would be ideal, however, we can approve on attached draft labeling. The sponsor is working with DDMAC at this point, so the letter can contain a statement to revise the promotions to be balanced and consistent with the approved labeling.

ACTION: Approved

The letter should describe the phase 4 commitments.

DIVISION DIRECTOR MEMO TO THE FILE

NDA: 20,193
DRUG: Elmiron (pentosan polysulfate) Oral Tablets
INDICATION: Treatment of Interstitial Cystitis
CATEGORY: Amendment Response to Non-Approval Letter
STATUS: Orphan Drug
SPONSOR: Baker Norton Pharmaceuticals, Inc.
SUBMITTED: August 31, 1995
COMPLETED: February 23, 1996

RELATED REVIEWS:

Chemistry - Stewart 10/11/95 & 12/5/95
Medical- Statistical:- Paserchia & Davi 1/31/96
Pharmacokinetics: - Gordin 9/1/92; Lee 1/29/96

BACKGROUND:

Elmiron is a polysaccharide based pentosan polysulfate that received Orphan Drug designation in 1985. It has a prolonged regulatory history that is well described in the introduction to the medical-statistical review and in the project manager resubmission summary. Key points of that history are 1) the NDA has received two non-approval letters (1993 & 1994); each of these letters requested one or more new studies, 2) new studies were not performed and 3) after a meeting with the sponsor and extensive coordination with the agency and sponsor's consulting statisticians, a prospectively designed retrospective analysis of the compassionate use data was performed.

Issues that were outstanding as of the October 28, 1994 non approval letter are briefly summarized below:

1. **Clinical:** One clinical trial was accepted (study # E002). A second clinical study was requested. The above compassionate use data is submitted for this purpose.
2. **Chemistry:** Additional information were requested on the drug substance stability at 18 months, drug substance stability control specification clarifications, three lots of drug product stability data and DMF letters of authorization to allow review of the DMF.

Other items that required attention, but were not the basis for the non-approval, included methods validation information and other procedural clarifications.

3. **Environmental Assessment:** Several pages of deficiencies were cited in the letter.
4. **Biopharmaceutics:** Requested additional information on the proposed for market formulation.

The sponsor has responded to these items and the application is now approval pending a safety update and related information, label revisions, pharmacokinetic clarifications and phase 4 commitments. Each will be addressed in the following sections:

CHEMISTRY: Based upon Dr. Stewart's review of the chemistry and Dr. Sager's review of the Environmental Assessment, Elmiron is approvable. A FONZI has been drafted. The inspection was acceptable on 12/12/94, a 10 day update is pending. The one remaining concern is that stability studies are needed on pentosan polysulfated when stored in the bulk drug storage bags from [redacted] This will be requested as a phase 4 commitment.

MICROBIOLOGY: Not applicable for this oral tablet.

PHARMACOKINETICS: Biopharmaceutics data continues to be of concern. Elmiron's formulation changed during the early stages of development. The first non-approval letter requested information and dissolution data on the 2 formulations. The second letter re-iterated a request for data on the new formulation and indicated that detailed information requests would be sent in a letter to the IND and recommended discussions with the reviewer at that time, Dr. Gordin.

Dr. Lee's review of 1/2/9/96 notes that new data were not submitted, the proposed for market drug was not studied and the assay validation data were not submitted. His review focuses on the question of what unit polymer was used in the original bio studies

Also, his review lists a number of questions that are derived from comments in the Investigator's Brochure and address newly submitted literature articles. These articles were addressed, additionally, in Dr. Paserchia's comments in the Medical-Statistical review page 6 - 9. However, the two new literature references (Losonczy and Jallad) provide limited data upon which to base conclusions.

Pentosan polysulfate (PPS) is a low molecular weight heparin that will be extensively metabolized by the liver. At present, there are insufficient data to characterize the metabolic profile or the active moiety. Some data are available to describe the parent compound. A team meeting was held to discuss this. It was determined that there are sufficient data upon which to develop a package insert with appropriate identification of where the deficiencies occur. Raw data for some of the sponsor's proposed statements are still needed and will be requested in reference to the package insert. Phase 4 commitments are needed to further characterize the active metabolites, the dose adjustment in hepatically impaired patients, effects on anticoagulation and drug-drug interactions with anticoagulants.

MEDICAL-STATISTICAL:

Baker Norton has amended the application with a compassionate use efficacy analysis. Now the full efficacy database consists of 2760 subjects (2629 {95.3%} patients and 131 {4.7%} volunteers). Of the 2629 patients, 130 {5%} were in clinical trials in the original application and 2499 {95%} were in the compassionate use data base. The med-stat review appendices C, table 1 & 2 are attached to this review (page 9) for quick reference and give the demographics of the

different studies. The exact numbers of men and women are not clearly provided; it appears, however, that in a subset of 2607 subjects for which numbers are available, there were 2338 (89.6%) women and 269 (10.4%) men. The average age is 45-46 years (approximately) with a range of 17 to 88 years.

Drs. Paserchia and Davi's joint medical-statistical review presents a cogent and useful discussion of the regulatory history, pharmacokinetics and pharmacodynamic considerations that are relevant to the clinical assessment of safety and effectiveness, a safety summary with reference to the original NDA review of 1991, a brief summary of the one study that was accepted for efficacy in 1994 (study E002) and the efficacy data from the current compassionate use patients. Their review should be read for details.

In essence, the critical efficacy question is whether the results of the prospectively designed retrospective analysis are adequate to stand as the second pivotal trial. The trial accepted in the October 28, 1994 non-approval letter was study E002. It demonstrated benefit in two of the six primary efficacy endpoints: improving bladder pain and the investigators global overall improvement. [NB: The other trial submitted at that time E001 was not accepted for efficacy because of the lack of independence. It provided inconclusive data on pain reduction; it can be used for safety.]

The compassionate use analysis evaluated the results of all of the 2499 patients who entered the program between 1986 and 1994. All patients baseline bladder pain and urgency and met the NIH criteria for interstitial cystitis by urinary cytology, cystoscopic evaluation, urinary cytology, and a bladder biopsy. Patient case report forms were completed every three months and contained information on pain urinary urgency, frequency, nocturia and adverse events. At the same time routine laboratory data and coagulation studies were obtained. The data were evaluated, openly, for the patients overall assessment of change in interstitial cystitis, change in pain, change in urgency, pain discomfort score, pressure to urinate, frequency and frequency of nocturia. These data were collected and recorded on case report forms at 3, 6, 9 and 12 months of treatment.

Although the protocol did not contain an a priori designation of a primary outcome variable, Drs. Davi & Paserchia selected pain because it is the key variable which changed in the E002 study. Additionally, the data were analyzed for a) trends in the secondary outcome measures which might improve and b) for baseline parameters that might predict an improvement with Elmiron (i.e., "responders" or those who continued to use Elmiron versus "non-responders" or those who stopped taking Elmiron).

Limitations of the database are: 1) the lack of a concurrent control, 2) the lack of independence of the patients over time (i.e., some patients in the one year treatment group are in the two and three year groups). Strengths of the analysis are: 1) designed by statisticians (FDA) before the data was seen, 2) patient as internal control, 3) rigorous collection of data prior to dispensing new drug, and 4) used all data -- not just the "best" data.

Results: Page 33, table 10 of the med-stat review (and attached to page 10 of this review) contains a life table of the number of patients who were available for analysis at different time points. The first column lists the number of months the patient was in the compassionate use

program. The second is the number of patients who enter any given time period. The "Active" column is the number that are anywhere in the time frame. For example for the group $0 < x < 3$ months, the number proceeding 1992 reflects all patients between 1 day and 3 months. The number in the " $3 < x < 6$ months" group in the column Cumulative Total Number of Patients (1192) is the number of patients who completed at least 3 months. That is the sample size for the 3 month evaluation. ["Young" patients are those who, at the time of the analysis cut off, had not dropped but did not complete the time frame and, therefore, are not eligible to be analyzed in that group.]

The primary analysis was based upon 3 month intervals over the 1st year. The other groups are considered in the safety analysis. Page 36 to 38 of the med-stat review contain the summary tables upon which the final outcome is based. There are two measures of pain that are represented below:

PAIN SCORES IN REFERENCE TO BASELINE COMPASSIONATE USE ANALYSIS, ELMIRON - N20,193			
Efficacy Parameter	3 months	6 months	12 months
Patient Rating of Overall Change in Pain (Recollection of difference between current pain and baseline pain)	N=1161 Median = 3 Mean = 3.44 CI: (3.37,3.51)	N=724 Median = 4 Mean = 3.91 CI: (3.83,3.99)	N = 516 Median = 4 Mean 4.25 CI: (4.16, 4.34)
Pain/Discomfort Score (Calculated difference between actual score at baseline and at the time point).	N=1440 Median = 1 Mean = 0.51 CI: (0.45, 0.57)	N=904 Median = 1 Mean = 0.66 CI: (0.61, 0.71)	N = 500 Median = 1.0 Mean 0.80 CI: (0.72, 0.87)

Of the above two measures, the Pain/Discomfort score is more robust. From these data it can be concluded that the patients recollection of change from baseline showed an average of 3.44 difference at three months and 3.91 at four months. These are within the confidence intervals. The actual calculated difference is consistent with a more modest change of one unit score.

In a companion analysis contained in the med-stat appendix A table 2, the data were checked to see if the baseline status affected the outcome (amount of improvement in the efficacy variable). As expected, the greatest change was seen in the most symptomatic patients. These are the patients who are driving the improvement scores. Patients with milder symptoms enter with low scores and there is little room for improvement.

[NB: In another analysis of baseline scores performed by the sponsor, there was a suggestion that baseline nocturia might predict the response ($p=0.03$); however, the statisticians multiple comparisons test did not confirm this.]

The next question was when patients are likely to improve and is there a point at which non-responders should stop Elmiron. This analysis is shown on the med-stat review page 40-41. These tables (13 a, b, & c) and attached to this review page 11-12 compare the change in pain/discomfort scores at 3 and 6, 9 & 12 months. The shaded portion of the table notes the

number of patients who had deteriorated or were not changed at 3 months (vertical axis) and compares them to the number of these who improved at each time point. In each of the 3 tables, approximately 13.2% to 15.4% of patients who did not change or were worse at 3 months, did improve by one of the next measurement points. A manual count was done to see if new patients were continuing to improve after 6 months and 33/93 (33%) new patients are part of the improved group at 9 months. This represents 33/391 (8.4%) patients who continued to 9 months and 33/1192 (2.7%) who continued past 3 months and 33/2499 (1.3%) of the patients who entered treatment with Elmiron. It is impossible to determine if these improvements are because of treatment or natural fluctuations in the disease.

Labeling of Elmiron should reflect the above in the clinical trials and recommend treatment that is consistent with the following: *If a patient is not improved at 3 months and if limiting adverse events have not occurred, then a trial of another 3 months can be given. A phase 4 commitment is needed to evaluate the maintenance regimen, to establish the optimal dose and to determine if the trends noted in the compassionate use data will predict those who will respond to treatment.*

SAFETY:

Elmiron's safety database consists of the two 3 month clinical trials in the earlier non-approved applications and the time point analysis of the compassionate use database. In the latter (as noted in the table on page 10), safety data is available on the following: 1192 (47.6%) through 3 months, 892 (55.6%) through 6 months, and 598 (23.9%) through 12 months. Overall exposures are attached to this review page 9 (reproduced from med-stat Appendix C). The med-stat review pages 15-30 contains the details of the safety summary.

Overall, the available data provides a comprehensive assessment of adverse events which are summarized in the table on page 14 (reproduced from the med-stat appendix B). These adverse events are for the 2506 patients for who data are available. The med-stat review discusses these in detail and the denominator for the different assessments changes based upon the data that are available for analysis. The sponsor's data presentation does not allow for a determination the number of patients who had at least one ADE. The most common events were diarrhea (3.9%), alopecia (3.9%) nausea (3.7%), headache (2.8%), rash (2.6%), dyspepsia (2.2%) and abdominal pain (2.0%).

A time of event analysis on page 25 of med-stat shows that a most of the events occur during the 1st 4 weeks.

Deaths did not occur in the 2 short clinical trials. In the compassionate use data there were 6/2629 (0.2%) over the 9 year period. These are discussed by Dr. Paserchia (p18-19) and the deaths appear to be related to underlying disorders such as cancer, stroke, peri-operative complications, and one unknown cause. A clear relationship to Elmiron can not be determined.

Serious events (33/2629 - 1.2%) were summarized by the sponsor and discussed by Dr. Paserchia. (See page 20 of the med-stat review and its appendix D for a summary table). The two patients that Dr. Paserchia selected as probably related to Elmiron had severe diarrhea with dehydration or

abdominal pain that was severe enough to cause hospitalization. In reviewing the data in appendix D, difficult to clearly attribute cause and effect. The adverse events are related to disorders that would occur in a population of 2000+ patients who are followed for several years (heart disease, stroke, cancer, etc.). Most of the events are probably related to concurrent illnesses. Those that could have a remote association include, the gastrointestinal pain, cramping, and all hematologic or bleeding events including stroke and hemoptysis. Speculatively, the worst case would be that small amounts of pentosan polysulfate were contributory. However, there is insufficient data upon which to make a determination. These should be noted in the package insert.

Laboratory data and vital signs information were not submitted with the compassionate use re-analysis. *These are needed before approval.* There are laboratory data available on the placebo controlled E002 trial of 141 patients. In these data, the following are noted:

	Elmiron		Placebo	
	Baseline (n=73) mean (std dev)	3 months (n=67) mean (std dev)	Baseline (n=74) mean (std dev)	3 months (n=64) mean (std dev)
Hematocrit	39.4 (2.8)	39.5 (2.8)	39.3 (3.3)	39.4 (3.3)
Hemoglobin	13.3 (0.9)	13.3 (0.9)	13.2 (1.2)	13.3 (1.3)
WBC	9.99 (1.97)	6.91 (1.87)	6.95 (1.83)	6.82 (1.86)
Platelets	299.4 (69.1)	302.4 (71.9)	298.2 (75.4)	305.2 (76.9)
PT (sec)	11.31 (0.96)	11.31 (1.14) (a)	11.4 (1.09)	11.39 (1.01)
PTT	28.42 (2.51)	29.4 (3.09) (b)	27.5 (3.04)	27.58 (3.06)
Alk Phos	66.0 (26.1)	68.7 (30.0)	70 (33.2)	71.6 (25.9)
SGPT	18.7 (11.5)	19.6 (9.7)	17.4 (8.2)	18.0 (10.2)
LDH	169.0 (69.7)	170.9 (79.4)	185.1 (82.6)	175.5 (72.9)
Bilirubin	0.47 (0.25)	0.46 (0.22)	0.47 (0.25)	0.49 (0.28)
BUN	13.8 (4.3)	13.5 (3.8)	13.5 (3.7)	13.4 (4.1)

(a) one patient increased the PT from 10.8 to 16.1 seconds

(b) one patients increased the PTT from 26.8 to 34.0 seconds

Based upon these data, it appears that there are sufficient data to support an approvable laboratory safety decision. *However, confirmations should be sufficient with the safety data response.*

DSI - Scientific investigations did not disqualify the data.

SAFETY UPDATE - Requested in the draft approvable letter

ASSESSMENT

Elmiron (pentosan polysulfate) is a low molecular weight heparin that is proposed for the treatment of chronic interstitial cystitis. Elmiron has Orphan Drug status for this disorder. Baker Norton has submitted sufficient safety and efficacy data to be approvable. However, the mechanism of action is still not clear. Also, the drug has anticoagulant effects that are similar to those of a related drug (Hemoclar) that was withdrawn from the market because of hematologic adverse events. It appears that the dose and route of administration are directly related to the differences in adverse event profiles of Elmiron and Hemoclar. The fact that Elmiron is given orally and is subject to first pass metabolism, means that the bioavailable levels are significantly lower. The complete lack of effect can not be ruled out, however. The active metabolites are not known and the blood levels at which anticoagulant effects occur are not known. Therefore, phase 4 commitments are needed to identify the active metabolites, the anticoagulant dose-response curve and whether dose adjustment is needed in hepatically impaired patients.

Elmiron is proposed in a 100 mg three times a day dose. This is reasonable to start. Whether this is needed for maintenance, whether it should be decreased in dose or daily frequency, whether it should be stopped at some point is not known. A phase 4 commitment is needed to determine the optimal dosing regimen.

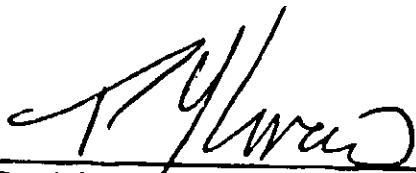
In addition to the above, other clarifications on the laboratory data, subpopulation analyses, chemistry and other data are noted below.

ACTION: Approvable

NEEDED ITEMS:

1. Submit a Compassionate Use study laboratory data and vital signs summary with means, standard deviation and ranges. Also, please submit contingency tables for clinically relevant pairs; e.g., hematocrit and hemoglobin, platelets and bleeding time or other obtained measures of coagulation, bilirubin and alkaline phosphatase, BUN and creatine.
2. Perform a demographic subset analysis for safety (age, race, gender) for the pivotal and compassionate use databases.
3. Submit the actual case report forms for the 33 serious adverse events reported in the compassionate use database.
3. Submit a Safety Update, including up to date adverse event reports and a review of world wide literature.
4. Devise a patient education sheet to be distributed at the time of marketing.

5. **Labeling Revisions are needed to develop new sections, revise the precautions, adverse events and overdose sections and to edit other sections (see draft of 2/23/96 for details)**
6. **Phase 4 Commitments:**

 2/23/96

Patricia Y. Love, M.D.
Director, Division of Medical Imaging &
Radiopharmaceutical Drug Products

Table 1
NDA 20,193 - Elmiron
NDA Database - Patient Enrollment/Discontinuation

N	Study E001		Study E002		Compassionate Use Program	Total	
	Elmiron	Placebo	Elmiron	Placebo		Elmiron	Placebo
Entered	54	56	76	75	2499	2629	131
Exposed to Elmiron	54	56	74	74	2499	2627	130
Completed	51	47	65	65	1192 ¹	1308	112
Drop-ADR	1	2	3	5	218 ²	222	7
Drop-Failed to Return	0	0	6	4	71 ²	77	4
Drop-Death	0	0	0	0	0 ²	0	0
Drop-Lack of Efficacy	0	1	0	0	344 ²	344	1
Drop-Other	0	0	0	0	407 ²	407	0
Drop-Investigator did not provide explanation	2	6	0	0	NA ³	2	6

1. Number of subjects who completed at least three months of Elmiron use during the compassionate use program.
2. Number of subjects who discontinued by three months during the compassionate use program.
3. For the compassionate use submission, the sponsor incorporated missing explanations into the "other" category.

Table 2
NDA 20,193 - Elmiron
NDA Database - #ADR's

Study Number	Type of Study	# Subjects (Placebo)	# Subjects (Elmiron)	# ADR's (Placebo)	# ADR's (Elmiron)
E001	Phase 3	56	54	9	9
E002	Phase 3	74	74	19	12
Compassionate Use Program	Open-label Uncontrolled	NA	2504	NA	1146 ¹
Total	NA	130	2632	28	1167

1. Number of ADR's which occurred within 12 months of Elmiron use during the compassionate use program.

Table 10 : Distribution of Patient Status by Total Length of Participation

Total Length of Participation	Cumulative Total Number of Patients	Active Patients		Inactive Patients	Discontinued Patients ¹
		Proceeding	"Young" Patients		
0 < x ≤ 3 mo.	2499	1192 (47.70%)	174	69	1064
3 < x ≤ 6 mo.	1192	892 (35.69%)	76	9	215
6 < x ≤ 12 mo.	892	598 (23.93%)	68	16	210
12 < x ≤ 18 mo.	598	461 (18.45%)	34	6	97
18 < x ≤ 24 mo.	461	355 (14.21%)	40	5	61
24 < x ≤ 36 mo.	355	225 (9.00%)	53	7	70
36 < x ≤ 48 mo.	225	145 (5.80%)	47	7	26
48 < x ≤ 60 mo.	145	86 (3.44%)	37	3	19
60 < x ≤ 90 mo.	86	0 ² (0.00%)	72	6	8
Total	NA	NA	601 (24.05%)	128 (5.12%)	1770 (70.83%)

1. The reasons for discontinuation are described in Table 11.

2. The number of patients proceeding to the next time interval was confined to being zero because although the compassionate use program is continuing, the data set had to be truncated at 90 months after the first patient was enrolled in order for analysis to be conducted.

Table 13a: Number of Subjects by each Level of Response (in Pain/Discomfort Rating) to Elmiron at Three Months Versus the Reported Response at 6 Months

Change (from Baseline) in Pain / Discomfort Score at Six Months					
Change (from Baseline) in Pain / Discomfort Score at Three Months		Deteriorated by 1 or 2 categories	No change	Improved by 1 or 2 categories	Total
	Deteriorated by 1 or 2 categories	23 (2.61%)	24 (2.73%)	3 (5.22%)	52 (5.92%)
	No change	32 (3.64%)	193 (21.96%)	111 (23.33%)	336 (38.23%)
	Improved by 1 or 2 categories	4 (.46%)	95 (10.81%)	392 (44.60%)	491 (55.86%)
	Total	59 (6.72%)	312 (35.50%)	508 (57.80%)	879 (100.00%)

Table 13b: Number of Subjects by each Level of Response (in Pain/Discomfort Rating) to Elmiron at Three Months Versus the Reported Response at 9 Months

Change (from Baseline) in Pain/Discomfort Score at Nine Months					
Change (from Baseline) in Pain / Discomfort Score at Three Months		Deteriorated by 1 or 2 categories	No change	Improved by 1 or 2 categories	Total
	Deteriorated by 1 or 2 categories	8 (2.84%)	14 (2.21%)	15 (7.05%)	37 (5.84%)
	No change	21 (3.32%)	123 (19.43%)	188 (43.90%)	232 (36.65%)
	Improved by 1 or 2 category	4 (.63%)	62 (9.79%)	298 (47.08%)	364 (57.50%)
	Total	43 (5.80%)	199 (31.44%)	391 (61.77%)	633 (100.00%)

Table 13c: Number of Subjects by each Level of Response (in Pain/Discomfort Rating) to Elmiron at Three Months Versus the Reported Response at 12 Months

Change (from Baseline) in Pain/Discomfort Score at Twelve Months					
Change (from Baseline) in Pain / Discomfort Score at Three Months		Deteriorated by 1 or 2 categories	No change	Improved by 1 or 2 categories	Total
	Deteriorated by 1 or 2 categories	5 (1.19%)	14 (3.34%)		23 (5.46%)
	No change	15 (3.57%)	97 (23.04%)		173 (41.09%)
	Improved by 1 or 2 categories	~~2~~ (.49%)	36 (8.55%)	187 (44.42%)	225 (53.45%)
	Total	22 (5.24%)	147 (34.92%)	262 (59.85%)	421 (100.00%)

Table 3: Death Reports Submitted during the Compassionate Use Study
 (adapted from Appendix F of the August 31, 1995 amendment and an October, 1995
 MedWatch report; n= -2700 because it comprises patients in the study through June, 1995)

ADR	Duration of Elmiron Use	Clinical History	Investigator's Opinion of Relation to Elmiron Use
death	8 months (3/91 - 11/91)	55 male w/ history of metastatic melanoma. Death occurred in 2/92	unrelated
death	4/92 to ?	72 male w/ history of hypertension, cardiovascular disease suffered a stroke and died in 1992 (date not provided).	unknown
death	30 months (1/91 - 7/93)	75 female w/ history of hypertension was diagnosed w/, & died 1/93 (?) of, poorly differentiated metastatic adenocarcinoma	remote
death	3 months (9/93 - 12/93)	74 female died 4 weeks post-gastroplasty/hiatal hernia repair; Elmiron stopped 2.5 months prior to surgery and not restarted	unrelated
death	75 months (1987 - 4/94)	68 female died of metastatic bronchogenic carcinoma; no h. norrhage	unrelated
death*	~ 16 months (3/94 - 6/95)	67 male w/ history of hypertension, ischemic heart disease, arrhythmias; meds- Procardia, Catapres, Inderal; died in 7/95- exact cause of death unknown	pending

Legend: * MedWatch report; Amendment 57 to IND

October 4, 1995

NDA 28-193

2 OF 7

8.0 APPENDIX B: Adverse Drug Reactions Grouped by Body System

ADH	Patients (n=2506)		Maximum Severity				Related to Elmiron?			Elmiron Continued?		
	#	%	Mild	Mod	Sev	Unk	Yes	No	Unk	Yes	No	Unk
Gastrointestinal												
diarrhea	98	3.9	19	18	8	53	67	8	23	47	44	7
nausea	93	3.7	12	17	11	53	60	11	22	40	47	6
dyspepsia	55	2.2	8	11	5	31	27	9	19	20	30	5
abdominal pain	51	2.0	6	9	1	32	22	9	20	16	30	5
SGOT elevated	7	0.28	0	1	0	6	1	2	4	3	4	0
SGPT elevated	6	0.24	1	2	0	3	4	1	1	1	5	0
LFT abnormality	26	1	6	4	0	16	17	1	8	10	15	1
Hematologic												
ecchymosis	18	0.72	8	2	0	8	11	3	4	6	11	1
thrombocytopenia	6	0.24	1	0	0	5	0	0	6	2	4	0
Urologic												
hematuria	13	0.52	2	3	0	8	4	5	4	6	7	0
Pulmonary												
epistaxis	8	0.32	2	0	1	5	5	0	3	1	7	0
Body as a Whole												
allergic reaction	5	0.24	1	1	0	3	3	2	0	2	3	0
face edema	3	0.12	1	0	0	2	2	0	1	1	2	0
generalized edema	1	0.04	0	0	0	1	0	0	1	0	1	0
death	3	0.12	0	0	1	2	0	3	0	0	3	0
Skin												
alopecia	98	3.9	17	21	3	57	60	9	29	44	52	2
rash	64	2.6	8	6	4	46	34	11	19	27	35	2
Neurologic												
headache	70	2.8	6	17	5	42	40	15	15	34	35	1
dizziness	28	1.1	0	6	3	19	20	3	5	10	17	1
parosmia	27	1.1	3	5	2	17	14	4	9	16	10	1

BRIEF DIVISION DIRECTOR'S ADDENDUM TO THE FILE

NDA: 20193
DRUG: ELMIRON
SPONSOR: BAXTER NORTON PHARMACEUTICALS, INC.
PURPOSE: INTERSTITIAL CYSTITIS
CATEGORY: AMENDMENT - ADDITIONAL CHEMISTRY DEFICIENCY RESPONSES
SUBMITTED: 2/14/94

RELATED REVIEWS:

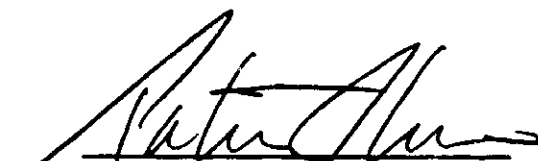
 PStewart (Chem) - 4/15/94

BACKGROUND:

Elmiron, oral pentosan polysulfate sodium capsules, are proposed for the treatment of interstitial cystitis. As noted in my February 16, 1994 memo to the file, the NDA was not approved in January, 1993 for a clinical, statistical and biopharmaceutical reasons. Responses to these deficiencies are still inadequate. After the 1993 NA letter was sent, the additional chemistry comments were sent in a separate letter. In February, 1994 the sponsor's responses to the chemistry deficiencies were received. These have subsequently been reviewed and, although acceptable in part, overall chemistry is still not approvable. Additional information is still needed to finalize the stability and dissolution assessment, and to clarify the methods validation (See P. Stewart's review). The Environmental Assessment is also inadequate. In June, 1993 the EER was acceptable. A 10-day update is pending at the time of this writing; it will be completed prior to final action.

ASSESSMENT:

The NDA remains not approvable. The residual chemistry and environmental assessment deficiencies should be added to the non-approval letter.

 6/01/94
Patricia Y. Loye, M.D.
Acting Division Director

BRIEF DIVISION DIRECTOR'S MEMO TO THE FILE

FEB 16 1994

NDA: 20193
DRUG: ELMIRON
SPONSOR: BAKER NORTON PHARMACEUTICALS, INC.
CATEGORY: AMENDMENT - RESPONSE TO NA LETTER OF 1/27/93
INDICATION: INTERSTITIAL CYSTITIS
SUBMITTED: JULY 9, 1993

RELATED REVIEWS:

Medical (Waymack) - 11/5/93
Statistical (Turney) - 9/30/93

BACKGROUND:

Elmiron, pentosan polysulfate sodium capsules for oral ingestion, is under development for the treatment of interstitial cystitis. An NDA for Elmiron was submitted on June 11, 1991. On January 27, 1993, the Elmiron NDA was not approved for lack of adequate clinical trials, the lack of supporting evidence for the time course to symptom relief, lack of distinction of drug effects from other influences and lack of an adequate bioavailability and pharmacokinetic assessments. The sponsor was advised to conduct new clinical and pharmacokinetic trials. In subsequent meeting with the sponsor on March 19, 1993 it was agreed that the sponsor could submit additional analyses to support their position that the existing database was adequate. Specifically the sponsor was to:

1. Perform additional analyses of their two pivotal trials (E001 and E002)
2. Analyze the compassionate use experience
3. Submit the case report forms or tabulations for E001 and E002
4. Design possible post marketing studies.

On July 7, 1993 the sponsor submitted responses to #1 and 2 above. While some of the sponsor's responses are adequate (documented the validity of the new intent to treat analysis and the comparability of the baseline values), there are still major deficiencies. The sponsor has reanalyzed the data based upon six primary outcome variables: 1) decrease in bladder pain based, 2) patient global assessment of improved pain, 3) decrease in urgency, 4) patient global assessment of urgency, 5) patient global and 6) investigator global. Many of these variables are redundant and multiple comparisons adjustments are needed. These data have been reviewed by the medical and statistical officers who both recommend non-approval. I am in agreement with their recommendation. The key issues are noted on the next page.

1. Lack of independence of the two trials submitted for substantial evidence. In trial E001 and E002 there are three investigators which account for 75% of all (110) the patients in trial E001 and 57% of the all (148) patients in trial E002.
2. Both trials fail to meet the level of statistical significance that would be required for multiple comparisons (Bonferroni correction to $p = 0.0130-0.016$). In trial E001, one of the six primary outcome variables (bladder pain) meet this criteria. In trial E002, two of the six primary outcome variables (the investigator global and patient global for overall improvement) meet this level of significance. There is a strong trend toward improvement in 3 of the 6 outcome variables.
3. Failure of the case report forms to support the scale used for analysis. The sponsor has used a 5 point scale (-1 to +4) where minus 1 = worse, zero = no change, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement and 4 = 100% improvement. The case report form (questionnaire), however, only asked for four responses (25, 50, 75 and 100% improvement).

Given the major flaws above, these data fail to demonstrate that the two trials are independent and present substantial evidence of effectiveness. Trial E002 is strongly supportive. Therefore, the request for two adequate and well controlled trials remains. It is possible that one very substantial trial along with trial E002 would be sufficient. However, if the trial is only marginally substantive, then assessment could still be confounded. The sponsor should be advised to submit protocols to the division for review and comment prior to their initiation.

In addition to the non-approval items, it is noted that the sponsor has not yet provided the compassionate use update not the bioavailability/pharmacokinetics data. These should be submitted with the full NDA re-submission.

ACTION: NOT APPROVABLE

REQUEST: 1. New clinical trials in a homogeneous population or in a population that is adequately randomized upon variables that could affect outcome (i.e., degree of residual void volume, existing urgency, etc.). The outcome variables should avoid

redundancy. A single primary outcome variable should be identified and the statistical plan should consider multiple comparisons

2. Adequate pharmacokinetic - bioavailability studies should be conducted.
3. All protocols should be reviewed by the division prior to their initiation.


Patricia Y. Love, M.D.
Acting Division Director

CC : Orig NDA
HFD - 160/Div File
HFD - 160/Div Dir/Love
HFD - 160/MO/Waymack
HFD - 713/Smith
HFD - 713/Turney
HFD - 161/Ree

Division Director's Review- NDA 20-193

NDA 20-193

Review date: 2/18/92

Sponsor: Baker Cummins Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, FL 33178

Drug: Elmiron (Pentosan polysulfate sodium)

Proposed Indication: Treatment of symptoms of Interstitial cystitis.

Related Reviews: MOR dated 12/4/92

Protocol: E-001

Design: Multicenter, randomized, double-blind comparison of 100 mg tid Elmiron vs placebo. The protocol was designed to include at least 120 patients.

<u>Enrolled Patients:</u>	<u>Enrolled</u>	<u>Completed</u>
1. * Phillip Hanno, MD	31	24
2. S. Grant Mulholland, MD	12	12
3. * C. Lowell Parsons, MD	27	25
4. * Grannum R. Sant, MD	24	23
5. David R. Staskin, MD	16	14
Total	110	98
Elmiron group:	54	51
Placebo group:	56	47

* Investigators for both E-001 and E-002.

An interim analysis of the data was obtained after about 50 patients had completed the 3 month double-blind period. This analysis indicated to the sponsor that about 100 patients would be sufficient for determining the safety and efficacy of Elmiron compared to placebo. The enrollment was stopped with 110 patients admitted into the study.

Reviewer's Comments:

1. *Investigators Hanno, Parsons and Sant were also investigators in protocol E-002.*
2. *The protocol did not enrolled the number of proposed patients. The interim analysis has not been submitted. The final analysis has not been adjusted to account for the interim look. The sponsor should provide an explanation.*

NDA 20-193 Elmiron

Efficacy Criteria: (in order of declared relevancy)

1. Patient's assessment of overall improvement compared to pretreatment.
2. Investigator's assessment of overall improvement.
3. Changes in pain and urgency.
4. Change in nocturia.
5. Change in frequency.
6. Change in average voided volume.

Overall Patient Evaluation - Number of patients (not available for evaluation)

		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>Total</u>		<u>P</u>
Elmiron	Better	8	0	4	1	2	15	(28%)	.04
	Not better	7(2)	6	9	11(1)	6	39(3)	(72%)	
Placebo	Better	2	1	1	2	1	7	(13%)	
	Not better	14(6)	5	13(2)	10	7	49(8)	(87%)	

Reviewer's Comments:

1. *The study was ended earlier than planned due to an interim analysis. The sponsor has not provided that analysis. Accounting for that analysis, the p value necessary to show statistical significance has not been stated. The level necessary to establish statistical significance is likely to be below 0.05 and therefore the reported value of 0.04 is considered marginal.*
2. *The success rate at center 1 is significantly different than the other sites and is responsible for the overall effect.*
3. *The effect of including "not available" patients in the 'Not better' category distorts the results because there is a higher percentage of "not available" patients in the placebo group.*
4. *Patient 5-9 failed to return to the Month 2 exam. It is not clear how a score was obtained for this patient.*

Overall Investigator Evaluation - Number of patients (not available for evaluation)

		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>Total</u>		<u>P</u>
Elmiron	Better	6	0	4	2	2	14	(26%)	.04
	Not better	9(1)	6	9	10(1)	6	40(2)	(74%)	
Placebo	Better	2	1	1	1	1	6	(13%)	
	Not better	14(6)	5	13(1)	11	7	50(7)	(87%)	

Reviewer's Comments:

1. *The study was ended earlier than planned due to an interim analysis. The sponsor has not provided that analysis. Accounting for that analysis, the p value necessary to show statistical significance has not been stated. The level necessary to establish statistical significance is likely to be below 0.05 and therefore the reported value of 0.04 is considered marginal.*
2. *The success rate at center 1 is significantly different than the other sites and is responsible for the overall effect.*
3. *The effect of including "not available" patients in the 'Not better' category distorts the results because there is a higher percentage of "not available" patients in the placebo group.*
4. *It is unclear how a score was obtained for patient 1-18, patient 3-25 or patient 5-9.*

Change in pain at month 3 - Number of patients

		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>Total</u>	<u>P</u>
Elmiron	Better	6	1	6	6	3	22 (46%)	.09
	Not better	7	5	7	4	3	26 (54%)	
Placebo	Better	5	3	2	3	0	13 (32%)	
	Not better	2	3	9	8	6	28 (68%)	

Reviewer's Comments: *No clinically significant difference was observed between groups.*

Change in Urgency at month 3 - Number of patients

		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>Total</u>	<u>P</u>
Elmiron	Better	5	0	4	8	3	20 (39%)	.24
	Not better	9	6	9	3	4	31 (61%)	
Placebo	Better	5	2	3	5	6	21 (46%)	
	Not better	4	4	9	7	1	25 (54%)	

Reviewer's Comments: *No clinically significant difference was observed between groups.*

Timing of Effect

<u>Patient with subjective improvement</u>	<u>Group</u>	<u>Month with Maximum pain Relief</u>	<u>Month with Maximum reduction in Urgency</u>
	E	2	2
	E	2	2
	E	2	2
	E	N/A	3
	E	3	3
	E	1	2
	E	3	3
	E	1	2
	E	1	3
	E	3	3
	E	3	3
	E	3	3
	E	3	2
	E	3	3
	E	2	3
	E	N/A	3
	P	3	2
	P	2	1
	P	1	1
	P	3	3
	P	2	1
	P	3	2
	P	2	3

Reviewer's Comments: *After reviewing the pain and urgency scores of patients who reported being better, the expected time for relief of pain or maximal reduction in urgency is shown above when it could be determined.*

Pain Relief:

<i>Elmiron:</i>	<i>Month 1- 23%</i>	<i>Month 2- 31%</i>	<i>Month 3- 46%</i>
<i>Placebo:</i>	<i>Month 1- 14%</i>	<i>Month 2- 43%</i>	<i>Month 3- 43%</i>

Reduction in Urgency

<i>Elmiron:</i>	<i>Month 1- 0%</i>	<i>Month 2- 40%</i>	<i>Month 3- 60%</i>
<i>Placebo:</i>	<i>Month 1- 43%</i>	<i>Month 2- 29%</i>	<i>Month 3- 29%</i>

The labeling statement "relief of symptoms in patients with interstitial cystitis may not be experienced until after 6 to 8 weeks of therapy" is not supported. There does not seem to be a significant difference in the time course between Elmiron or placebo patients who at the end of the trial are considered to have obtained relief of symptoms.

Protocol: E-002

Design: Multicenter, randomized, double-blind comparison of 100 mg tid Elmiron vs placebo. The protocol was designed to include at least 120 patients. The main difference between this study and the first was that in the first study (E-001) patients were to have failed a previous therapy. Previous therapy was not a strict entry criteria for this study.

Enrolled Patients:		Enrolled	Completed
1.	* C. Lowell Parsons, MD	29	27
2.	* Phillip Hanno, MD	33	27
3.	George Benson, M.D.	9	8
4.	Stacy J. Childs, M.D.	32	28
5.	Suzanne Frye, M.D.	8	8
6.	George Webster, M.D.	14	13
7.	* Grannum R. Sant, MD	23	19
Total		148	130
Elmiron group:		74	65
Placebo group:		74	65

* **Reviewer's Comments:** *Investigators Parsons, Hanno and Sant were also investigators in protocol E-001.*

Efficacy Criteria: (in order of declared relevancy)

1. Patient's assessment of overall improvement compared to pretreatment.
2. Investigator's assessment of overall improvement.
3. Changes in pain and urgency.
4. Change in nocturia.
5. Change in frequency.
6. Change in average voided volume.

Overall Patient Evaluation - Number of patients (not available for evaluation)

		1	2	3	4	5	6	7	Total		P
Elmiron	Better	10	1	2	5	1	1	4	24	(32%)	.02
	Not better	5(1)	15(2)	3	11(2)	3	5	8(2)	50(7)	(68%)	
Placebo	Better	2	1	0	5	2	2	0	12	(16%)	
	Not better	12(1)	16(4)	4(1)	11(1)	2	6	11(2)	62(9)	(84%)	

Reviewer's Comments:

1. *The success rate at center 1 is significantly different than the other sites and is responsible for the overall effect.*
2. *The effect of including "not available" patients in the 'Not better' category distorts the results because there is a higher percentage of "not available" patients in the placebo group.*

Overall Investigator Evaluation - Number of patients (not available for evaluation)

		1	2	3	4	5	6	7	Total		P
Elmiron	Better	11	1	1	5	1	1	7	27	(36%)	.003
	Not better	4(1)	15(2)	4	11(2)	3	5	5(1)	47(7)	(64%)	
Placebo	Better	2	1	0	4	2	2	0	11	(15%)	
	Not better	12(1)	16(3)	4(1)	12(1)	2	6	11(1)	63(9)	(85%)	

Reviewer's Comments:

1. *The success rate at center 1 is significantly different than the other sites and is responsible for the overall effect.*
2. *The effect of including "not available" patients in the 'Not better' category distorts the results because there is a higher percentage of "not available" patients in the placebo group.*
3. *It is unclear how there were evaluations for patients
patients did not have overall patient evaluations.* *These*

Change in pain at month 3 - Number of patients

		1	2	3	4	5	6	7	Total	P
Elmiron	Better	9	9	3	9	2	5	5	42 (66%)	.06
	Not better	5	5	1	4	2	0	5	22 (34%)	
Placebo	Better	5	8	0	11	2	3	4	33 (52%)	
	Not better	7	5	3	4	1	5	5	30 (48%)	

Reviewer's Comments: *No clinically significant difference was observed between groups.*

Change in Urgency at month 3 - Number of patients

		1	2	3	4	5	6	7	Total	P
Elmiron	Better	12	6	3	8	2	3	5	39 (61%)	.03
	Not better	2	8	1	5	2	2	5	25 (39%)	
Placebo	Better	4	6	0	8	3	3	4	28 (43%)	
	Not better	9	7	3	7	1	5	5	37 (57%)	

Timing of Effect

<u>Patient with subjective improvement</u>	<u>Group</u>	<u>Month with Maximum pain Relief</u>	<u>Month with Maximum reduction in Urgency</u>
	E	2	2
	E	3	3
	E	3	3
	E	2	2
	E	3	3
	E	1	1
	E	N/A	2
	E	3	3
	E	3	3
	E	3	3
	E	3	2
	E	3	3
	E	2	1

Timing of Effect (continued)

Patient with subjective improvement	Group	Month with Maximum pain Relief	Month with Maximum reduction in Urgency
	E	3	3
	E	1	2
	E	3	3
	E	1	2
	E	N/A	3
	E	1	1
	E	1	2
	E	3	2
	E	3	3
	E	3	3
	E	2	1
	P	N/A	N/A
	P	3	3
	P	2	3
	P	2	3
	P	1	3
	P	3	3
	P	3	3
	P	1	1
	P	3	2
	P	1	1
	P	3	3
	P	1	3

Reviewer's Comments: *After reviewing the pain and urgency scores of patients who reported being better, the expected time for relief of pain or maximal reduction in urgency is shown above when it could be determined.*

Pain Relief:

<i>Elmiron:</i>	<i>Month 1- 23%</i>	<i>Month 2- 18%</i>	<i>Month 3- 59%</i>
<i>Placebo:</i>	<i>Month 1- 36%</i>	<i>Month 2- 18%</i>	<i>Month 3- 45%</i>

Reduction in Urgency

<i>Elmiron:</i>	<i>Month 1- 17%</i>	<i>Month 2- 33%</i>	<i>Month 3- 50%</i>
<i>Placebo:</i>	<i>Month 1- 18%</i>	<i>Month 2- 9%</i>	<i>Month 3- 73%</i>

The labeling statement "relief of symptoms in patients with interstitial cystitis may not be experienced until after 6 to 8 weeks of therapy" is not supported. There does not seem to be a significant difference in the time course between Elmiron or placebo patients who at the end of the trial are considered to have obtained relief of symptoms.

Conclusions:

1. The sponsor has evaluated different parameters on different sets of patients. The analysis of some variables treat missing data as "not better." When other parameters are evaluated, patients without pain on entry are excluded.
 - a. A per protocol analysis should be provided for all variables. This analysis should exclude patients without pain on entry and exclude patients at time points when no evaluation was performed.
 - b. An intent to treat analysis should be provided for all variables. This analysis should include all patients enrolled into the study and followed for all time points possible.
 - c. If the results of the per protocol analysis and the intent to treat analysis are different, the sponsor should provide an explanation.
2. Based on the analyses submitted to date, there appears to be significant investigator interaction. The results obtained by the first investigator listed in each study are significantly different than the results obtained for each of the other investigators in the studies.
3. The instructions on the case report forms were to "circle the number that best describes" the rating. Only whole numbers are included on the scale and descriptions of only the odd numbers are given. The sponsor reports scores between these whole numbers. It is unclear how these half numbers were obtained. The sponsor should submit a copy of all case report forms so that a comparison of the case report forms and the reported scores can be made.
4. It is not clear how the sponsor intends to support the statement "relief of symptoms in patients with interstitial cystitis may not be experienced until after 6 to 8 weeks of therapy."
5. Labeling will need to be re-evaluated following the above recommended re-analyses.

Recommendations:

The application as submitted is not recommended for approval. It is recommended that the following items be addressed by the sponsor if the application is resubmitted.

The application as submitted lacks substantial evidence consisting of adequate and well-controlled investigations, as defined in 21 CFR 314.126 that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically, the analysis of the results of the submitted studies are not adequate to assess the effects of the drug.

1. The analysis does not assess the comparability of the test and control groups with respect to pertinent variables and the effects of any interim data analyses performed. If the application is resubmitted, it is recommended that the following analyses be submitted:
 - a. A "per protocol" analysis should be provided for all variables. This analysis should exclude patients without pain on entry and exclude patients at time points when no evaluation was performed.
 - b. An "intent to treat" analysis should be provided for all variables. This analysis should include all patients enrolled into the study and followed for all time points possible.

If the results of the per protocol analysis and the intent to treat analysis are different, an explanation should be provided.

If the drug product is not considered to be equally effective in all patients with interstitial cystitis then appropriate subgroup analyses should be performed which identify sub-populations in which the drug product is effective.

2. Additional support is needed to justify the statement that the relief of symptoms may not be experienced until after 6 to 8 week of therapy. The time course related to the relief of symptoms observed in studies E-001 and E-002 appears equivalent to the relief of symptoms observed with the placebo therapy. This relief of symptoms would therefore seem to be representative of the natural history of the disease and not related to therapy.

3. The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences. Based on the analyses submitted to date for studies E-001 and E-002, there appears to be significant investigator interaction. The results obtained by the first investigator listed in each study are significantly different than the results obtained by each of the other investigators in the studies. In the absence of an adequate explanation for these differences, studies E-001 and E-002 cannot be considered to be adequate and well-controlled. It is recommended that an additional clinical investigation utilizing investigators not included in previous studies be conducted and submitted as part of any resubmission of this application.

In addition, if the application is resubmitted, complete case report forms and tabulations for all patients in studies E-001 and E-002 will be required.


Wiley A. Chambers, M.D.
Acting Director, HFD-160

cc: Orig NDA 20-193
HFD-160
HFD-161/CSO/Rhee
HFD-160/CHEM/Stewart
HFD-160/PHARM/Wilson
HFD-160/MO/Rodriguez
HFD-160/SMO/Keneally

7-22
Division Director's Comments on NDA 20-193

NDA 20-193

Review date: 2/18/92

Sponsor: Baker Cummins Pharmaceuticals, Inc.

Drug: Elmiron (Pentosan polysulfate sodium)

Proposed Indication: Treatment of symptoms of Interstitial cystitis.

Related Reviews: MOR dated 12/4/92

The following comments are related to the Medical Officer's Review dated December 4, 1991 and need further discussion:

1. **Page 27** The use of an interim analysis needs to be discussed. How was the decision to stop enrollment made?
2. **Page 27** Twelve patients did not complete the study.
 - One patient withdrew because of diarrhea.
 - One patient withdrew because of joint pain.
 - One patient withdrew due to headache, severe mood swings.
 - One patient withdrew due to lack of effect.

Why did the other eight patients not complete the study?
3. **Page 33** Why were patients who failed to return determined to have a "not better" score on pain and also on urgency? The sponsor's October 3, 1991 submission does not identify these patients as "not better."
4. **Page 38** The placebo group of investigator 5 lists 9 patients. There were only eight enrolled. Where did the ninth patient come from?
5. **Page 42** The review states that the protocol was projected to have 100 to 120 patients. On Page 43 of the review, it states that the number of planned patients was 130 to 140 patients. Which is correct?
6. **Page 46** Dr. Sant is listed as qualified to be an investigator per his submitted CV and is also included in the list of investigators for whom CVs were not submitted. This should be clarified.
7. **Page 55** What was the level of statistical significance for improvement in urgency?
8. **Page 58** What was the level of statistical significance for improvement in volume?
9. **Page 60-62** What was the level of statistical significance for the variables presented?

10. Page 69 Why is there not complete information on CL Parsons and SG Mulhollands published study? This study should either be completely reported in the NDA or in Parson's IND? Either way, complete information should be available.
11. Page 88-89 The difference between Investigator 1 and the rest of the group is more important than the difference in the total daytime volume score. The fact that this one investigator carries the efficacy should be clearly identified in the review. This is true of both studies.
12. Page 92-93 A more complete discussion of the first two paragraphs in the proposed "Clinical Pharmacology" section is needed. The animal studies, if validated should be included in an animal studies section, not the clinical pharmacology section. The studies should also be adequate and well-controlled if they are to be included.

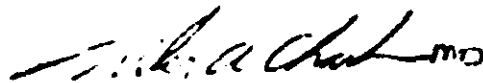
The Adverse Reaction section of the labeling is listed as satisfactory. Why are Adverse Experiences which were seen only in the placebo group included in the labeling of product?

The Pregnancy subsection of the Precautions section does not conform to 201.57 and should be addressed in the review.

The review should specifically address the evidence in the NDA to support the statement in the indications section "Continuing long term therapy may be required for persistent relief of symptoms."

The overdose section is listed in the review as satisfactory. The proposed labeling does not include any of the components listed in 201.57(i). This should be clarified.

13. There is no discussion about effect of treatment in periods of less than three months. Patients were evaluated monthly.
14. Study E-002 continued for a year. The review should include information about the extended use (i.e., number of patients, efficacy measurements, drop outs with reasons, and adverse events).


Wiley A. Chambers, M.D.
Acting Director, HFD-160

cc: Orig NDA 20-193
HFD-160
HFD-161/CSO/Rhee
HFD-160/MO/Rodriguez
HFD-160/SMO/Keneally

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Group Leader's Comment

Interstitial cystitis is a disease for which there is no known effective therapy. It is relatively uncommon, occurring most frequently in females, very rarely in males. Due to this uncommon incidence, the drug that is the subject of this NDA has been granted orphan status.

Dimethyl sulfoxide (DMSO), administered by local instillation into the urinary bladder, has been approved (NDA 17-728, appr. 9/19/75) for symptomatic relief in this condition, but efficacy response in most instances has been extremely disappointing. In addition to this poor efficacy response, administration requires vesical catheterization, an invasive procedure having the potential of compounding the primary disease with bacterial cystitis.

Pentosan polysulfate sodium (Elmiron) has been reported in uncontrolled studies and in numerous testimonial statements to be effective for the relief of symptoms of interstitial cystitis, an emotionally and socially debilitating symptom complex. The present application reports two controlled clinical trials of the safety and efficacy of this drug for this indication.

This application is reasonably well organized and presented, although some of the tables are confusing and contain what appear to be inaccuracies. The single most glaring deficiency is the protocol violation for each of the two studies by which patients who did not fulfill the entrance requirement for pain were admitted. Pain is a major component of this symptom complex and, while characteristically waxing and waning, is present in the overwhelming majority of patients suffering with true interstitial cystitis. The entrance criteria for each study specifically require pain as a condition of admission.

As pointed out in the Medical Officer's review of these studies, there appears to be some advantage of the active medication over the placebo, even in this condition in which a high incidence of placebo response has long been recognized.

The reviewing statistician has made the important observation that in each of the studies herein presented, elimination of the results from one of the centers all but destroys the statistical significance of the result of that study. The medical reviewer has indicated that one of these two investigators is known to have a financial interest in this drug. Because of the strong influence of these centers on the outcome, Scientific Investigations has been requested to audit the records of these centers for these studies.

Among the data submitted with this application there were no CRF's and no tabulation of any individual patient responses. Lack of this type of material rendered impossible the identification of individual subjects who may have had a particularly good response to therapy. In the absence of other reliable therapy, identification of such a sub-set of patients would simplify the decision of whether to recommend approval of the drug for that limited population. Therefore, on September 9, 1991, the reviewing Medical Officer requested this type of tabulation from the sponsor. Review of this material has not been helpful in the identification of a subset of patients who have demonstrated an especially outstanding response.

There are few or no significant concerns about the safety of this drug. To date, there have been no reports of serious side effects. Adverse experiences that have been reported have been minor and self-limited and may be easily and clearly addressed in the labeling.

Were there an effective alternative therapy for this disease, the present application could not be recommended for approval due to the major protocol violation in each of the two studies and to the lack of totally convincing clinical or statistical evidence of efficacy. It does appear, however, that a few interstitial cystitis patients do benefit with institution of this treatment regimen. Denial of the opportunity for this benefit, even to a few, does not appear to be justified in view of the apparent lack of serious or lasting adverse reactions.

Assuming that the Division of Scientific Investigations finds no irregularities in the data collected by Drs. Parsons and Hanno, it is recommended that NDA 20-193 is clinically approvable with the major changes in the Indications and Usage section of the package insert as recommended by Dr. Rodriguez. Should there be irregularities in either of the studies under investigation, this recommendation will, in my opinion, require reversal.



John C. Kenealy 12/13

 John C. Kenealy, M.D.

*See Div Director's Review
 on Comments dated 2/18/92*

DEPUTY DIRECTOR'S MEMORANDUM TO FILE:

• **ADDENDUM TO CLINICAL REVIEW**

NDA: 20-193

DRUG: Elmiron® (pentosan polysulfate sodium) capsules

ROUTE OF ADMINISTRATION: Oral

STRENGTH(S): 100 mg

PROPOSED INDICATION: Treatment of Interstitial Cystitis*

TYPE OF SUBMISSION: Amendment to a pending application (Response to Approvable Letter)

STATUS: Orphan Drug

SPONSOR: Baker Norton Pharmaceuticals, Inc.

SUBMITTED: 10 April 1996

COMPLETED: 26 September 1996

REVIEWER: Victor F.C. Raczowski, M.D., M.S. *Victor F.C. Raczowski 9/26/96*

This memorandum explains the rationale for the use of the numerator of 722 patients as the number of patient who improved by one or two categories at three months in the physicians' usage study. Previously, the number 491 was used, extracted from Table 13a in the Clinical/Statistical review dated 1/31/96.

As shown in the table on the next page (obtained from the statistician, Dr. Ruthanna Davi), at three months 191 patients who had a baseline pain/discomfort score of 2 improved by one category (to a score of 1). Similarly, 381 patients with a baseline score of 3 improved by one category (to a score of 2 at three months), and 150 patients with a baseline score of 3 improved by two categories (to a score of 1 at three months).

The sum of 191, 150, and 381 is 722, reflecting the total number of patients at three months who improved by one or two categories.

Conversely, the number 491 in Table 13a should not be used, because this includes the three-month data from only those patients who continued to six months.

Recommendation: The clinical trials section of the package insert has been modified accordingly.

Question: Indicate what the baseline pain/discomfort scores were in reference to patients' three months pain/discomfort scores.

Pain/Discomfort Score at baseline: N = 2352
 Mean = 2.52
 CI: (2.49, 2.55)
 Median = 3

Pain/Discomfort Score		
Baseline	Three Months	Number of Patients (N = 2499*)
missing	missing	77
	1	22
	2	32
	3	15
1	missing	68
	1	69
	2	25
	3	8
2	missing	287
	①	191
	2	241
	3	62
3	missing	557
	①	150
	②	381
	3	312

* Two patients were not included in this table due to apparent data entry errors.

Table 13a: Number of Subjects by each Level of Response (in Pain/Discomfort Rating) to Elmiron at Three Months Versus the Reported Response at 6 Months

Change (from Baseline) in Pain / Discomfort Score at Six Months					
Change (from Baseline) in Pain / Discomfort Score at Three Months		Deteriorate d by 1 or 2 categories	No change	Improved by 1 or 2 categories	Total
	Deteriorated by 1 or 2 categories	23 (2.61%)	24 (2.73%)	52 (5.92%)	52 (5.92%)
	No change	32 (3.64%)	193 (21.96%)	336 (38.23%)	336 (38.23%)
	Improved by 1 or 2 categories	4 (.46%)	95 (10.81%)	392 (44.60%)	491 (55.86%)
	Total	59 (6.72%)	312 (35.50%)	508 (57.80%)	879 (100.00%)

DEPUTY DIRECTOR'S MEMORANDUM TO FILE:

- **SUMMARY OF SPONSOR'S RESPONSE TO APPROVABLE LETTER**
- **CLINICAL REVIEW**

NDA: 20-193

DRUG: Elmiron® (pentosan polysulfate sodium) capsules

ROUTE OF ADMINISTRATION: Oral

STRENGTH(S): 100 mg

PROPOSED INDICATION: Treatment of Interstitial Cystitis

TYPE OF SUBMISSION: Amendment to a pending application (Response to Approvable Letter)

STATUS: Orphan Drug

SPONSOR: Baker Norton Pharmaceuticals, Inc.

SUBMITTED: 10 April 1996

COMPLETED: 23 September 1996

REVIEWER: Victor F.C. Raczkowski, M.D., M.S.

RELATED REVIEWS AND MEMORANDA:

Chemistry: Stewart 10/11/95 & 12/05/95

Joint Medical-Statistical: Paserchia & Davi 01/31/96

Statistical: Davi 07/16/96

Clinical Pharmacology and Biopharmaceutics: Gordin 09/01/92; Lee 01/29/96 & 09/16/96 (draft)

Division Director: Love 02/23/96

BACKGROUND:

Elmiron® (pentosan polysulfate sodium) was designated an Orphan Drug for the treatment of interstitial cystitis in August 1985. Its regulatory history has been summarized in the Division Director's Memorandum to the File (02/23/96), and has been detailed both in the introduction to the joint Medical-Statistical review (01/31/96) and in the project manager's Administrative Summary (titled "Elmiron Resubmission Summary Addendum").

Briefly, the sponsor received two not-approvable letters for this NDA on 01/27/93 and 10/28/94, largely because of the lack of a confirmatory trial demonstrating the efficacy and safety of Elmiron in the treatment of patients with interstitial cystitis. The sponsor subsequently performed a retrospective analysis of data obtained between 1986 and 1994 in approximately 2500 patients with interstitial cystitis.¹ After review of these data and related submissions, the FDA sent an approvable letter to the sponsor on 03/01/96. The current submission (04/10/96) contains a response by Baker Norton Pharmaceuticals, Inc. to the issues raised in that approvable letter.

The issues identified in the approvable letter are briefly summarized immediately below, and will subsequently be discussed in more detail:

1. **Clinical/Statistical:** The clinical/statistical issues were divided into six items. Four of these items requested additional safety analyses and documentation. The fifth item asked the sponsor to

¹ In this memorandum, I will refer to this as the "physicians' usage program" or the "physicians' usage study." The sponsor often refers to this as the "compassionate-use study."

devise a Patient Package Insert, and the last requested that the sponsor clarify the chemical similarities and differences of Hemoclar² and Elmiron.

2. **Biopharmaceutics/Pharmacokinetics:** As requested in previous non-approval letters, the sponsor was asked to validate the assay used in the pharmacokinetics studies and to provide the corresponding raw data tables, including descriptive statistics.
3. **Labeling:** Baker Norton Pharmaceuticals, Inc. was asked to submit draft labeling identical to the enclosed marked-up draft.
4. **Phase 4:** The FDA sought commitments for phase 4 studies that were grouped into five categories:

Clinical/Statistical:

For clarity, in this section the verbatim wording from the approvable letter has been reproduced in italics. Some items will be discussed in detail, as this memorandum also serves as the clinical review.

1. *Please submit a tabular summary of laboratory data and vital signs derived from the open label physician's usage study (referenced in your submission as a compassionate use study). This*

As summarized in the Clinical/Statistical review, Hemoclar is a brand of pentosan polysulfate sodium that was manufactured and marketed in France from 1961 to 1994. It was administered sublingually to treat hyperlipoproteinemias, and by intramuscular or subcutaneous injection for anticoagulation. Hemoclar was withdrawn from the market by French officials because of an unacceptable risk/benefit profile (especially reports of delayed immunologic thrombocytopenia).

should include means, standard deviation, and ranges (provide laboratory test normal ranges and highlight any abnormal test results).

Also, please submit contingency tables for clinically relevant pairs (e.g., hematocrit and hemoglobin; platelets and bleeding time or other obtained measures of coagulation; bilirubin and alkaline phosphatase; BUN and creatine (sic)).

Vital signs were not collected as part of the physicians' usage program. However, laboratory data were obtained on some patients for up to 27 1/2 months and were included in this submission. Laboratory measures that were assessed included the following: glutamate-oxalate transaminase (SGOT), lactic dehydrogenase (LDH), alkaline phosphatase, creatinine, total bilirubin, hematocrit, hemoglobin, white blood cell count, platelet count, prothrombin time (PT), and partial thromboplastin time (PTT). Laboratory specimens within the intervals indicated in Table 1 were included in the tabulations whenever available. If multiple specimens for a patient were present during an interval, the value of the analyte that was most deviant among the specimens was chosen to represent the patient in the interval except at baseline at which time the most recent value was chosen.

As shown in the Table 1, 2,810 patients were exposed to Elmiron. Only about 1% of the patients had laboratory evaluations before three months. At three months, 43-48% of the patients had at least one laboratory test performed. Between three and 24 months, 18-30% of the patients had at least one laboratory test performed.

Table 1
Distribution of Patients with Available Laboratory Specimens at Specified Time Points
(n=2810)

Time Point	Interval (months)	Minimum and maximum number (%) of patients with at least one available specimen for at least one laboratory test*			
		Minimum		Maximum	
Baseline	[-6 to 0)	NA	(NA)	NA	(NA)
< 3 months	[0 to 1.5)	36	(1%)	40	(1%)
3 months	[1.5 to 4.5)	1221	(43%)	1339	(48%)
6 months	[4.5 to 7.5)	773	(28%)	850	(30%)
9 months	[7.5 to 10.5)	584	(21%)	652	(23%)
12 months	[10.5 to 16.5)	610	(22%)	678	(24%)
24 months	[16.5 to 27.5)	508	(18%)	555	(20%)

*NA = not available (i.e., data not provided in this submission). See the text for a summary of laboratory tests that were performed.

Reviewer's Analysis:

The mean and median changes from baseline did not appear to change systematically from baseline after patients were exposed to Elmiron for any of the laboratory tests. This conclusion is based on visual

examination of the data (descriptive statistics, box plots) for each of the laboratory tests. A visual evaluation of systematic changes from baseline based on other percentiles (i.e., 10th, 25th, 75th, 90th) was uninterpretable because both the duration of the intervals (as shown in Table 1) and the number of specimens obtained in any interval varied. Stated differently, the data were not normalized for these variables. Hence, real changes of laboratory values from baseline could not be distinguished from drifts from baseline caused by increased variability of the data.

Individual data points (e.g., for outliers or extreme outliers) were not provided in the box plots. Therefore, these visual displays were not useful for identifying large changes from baseline that may have occurred in only a few individuals.

As summarized in Tables 2-5, while on therapy several patients developed clinically-significant exacerbations (increases or decreases) in grade of their laboratory values. Table 6 shows the number of patients whose laboratory values were known to return to their baseline grade or not. The major features of these tables are summarized below:

- a) **Liver function tests:**³ A number of patients developed clinically-significant increases of their liver function tests (i.e., to at least twice the upper limit of normal [ULN] for SGOT, LDH, and alkaline phosphatase; or to at least to 1½ times the ULN for total bilirubin). Thirteen patients developed clinically significant increases of SGOT, three of LDH, one of alkaline phosphatase, and seven of total bilirubin. The times when these increases first occurred were distributed across all times; (e.g., in some patients increases occurred within the first three months of Elmiron therapy, in others as late as after 24 months of therapy). Given the shrinking sample size over time, the incidence of clinically-significant increases in liver function tests may actually be increasing over time. In about half of the cases, the elevated values of liver function tests returned to the baseline grade. In the remaining half of the cases, either the value did not return to baseline or else follow-up was inadequate to make a determination.
- b) **Renal function tests:** Two patients developed clinically-significant increases of their serum creatinine (i.e., to at least to 1½ times the ULN). The increase first occurred at three months in one patient and at six months in another. The serum creatinine returned to the baseline grade in one patient, but in the other follow-up was inadequate to make a determination.
- c) **Hematological tests:**⁴ Most patients with clinically-significant changes in hematological tests manifest depression in the hematological index under consideration. For example, all patients with clinically-significant changes in hemoglobin or hematocrit had decreases (as opposed to increases) in these parameters (i.e., a drop of hemoglobin to at least 10/12 times the lower limit of normal [LLN], or a drop in hematocrit to at least 30/37 times the LLN). Similarly, the large majority (i.e., 37/43 = 86%) of patients with clinically-significant changes in white blood cell (WBC) count had a decrease (i.e., a drop of the WBC count to at least 3/4 the LLN). Some patients (i.e., 6/43 = 14%), however, did have clinically-significant increases in their WBC count (i.e., an increase of the WBC count to at least 1.5 times the ULN).

Although the numbers of cases were too small to draw definite conclusions, clinically-significant drops in hemoglobin or hematocrit appeared to be more common after prolonged exposure to

For purposes of these analyses, SGOT, LDH, total bilirubin, and alkaline phosphatase are regarded as liver function tests.

⁴ For purposes of these analyses, hematologic tests include hemoglobin, hematocrit, and white blood cell count.

Elmiron (e.g., 12-24 months) than after exposure for less than 12 months. Clinically-significant drops in WBC count appeared to be evenly distributed across times. Again, given the shrinking sample size over time, the incidence of clinically-significant decreases in hematocrit, hemoglobin, and WBC count may be increasing over time. In most cases of these clinically-significant changes of hematological indices, a return to the baseline grade was not documented. Hence, the reversibility of these changes has not been demonstrated.

- d) Coagulation tests⁵ Only one patient had a documented clinically-significant decrease (i.e., to at least 2/3 times the LLN) of the platelet count after exposure to Elmiron. This patient's platelet count decreased to 52,000/ μ L within three months of exposure to Elmiron. This depression was reversible. Four patients were identified who had clinically-significant increases in their PTTs (i.e., to at least 1.25 times the ULN). In no case was a return to the baseline grade documented. No patients were identified who had clinically-significant increases in PT (i.e., to more than 1.75 times the ULN).

⁵ For purposes of these analyses, coagulation tests include platelet count, PT, and PTT.

**Table 2:
Numbers of Patients with Clinically-Significant Increases in Liver Function Tests**

Test	Baseline Value	Baseline N	Time at which Clinically-Significantly Deviant Value was First Noted				
			3 months	6 months	9 months	12 months	24 months
SGOT							
	WNL	9	2	2	2	2	1
	I	3	1	-	-	1	1
	II	1	-	1	-	-	-
LDH							
	WNL	2	1	-	-	1	-
	I	1	-	-	1	-	-
	II	0	-	-	-	-	-
Alkaline phosphatase							
	WNL	0	-	-	-	-	-
	I	1	1	-	-	-	-
	II	0	-	-	-	-	-
Total Bilirubin							
	WNL	3	2	1	-	-	-
	I	1	-	-	-	-	1
	II	2	1	-	1	-	-
	U	1	1	-	-	-	-

- WNL = laboratory value within normal range at baseline
- I = laboratory value above normal range at baseline (but not to a clinically-significant degree)
- II = laboratory value elevated at baseline to a clinically-significant degree
- U = laboratory value unknown at baseline

Table 3
Numbers of Patients with Clinically-Significant Increases in Serum Creatinine

Test	Baseline Value	Baseline N	Time at which Clinically-Significantly Deviant Value was First Noted				
			3 months	6 months	9 months	12 months	24 months
Creatinine							
	WNL	-	-	-	-	-	-
	↑	2	1	1	-	-	-
	↑↑	-	-	-	-	-	-

- **WNL = laboratory value within normal range at baseline**
- **↑ = laboratory value above normal range at baseline (but not to a clinically-significant degree)**
- **↑↑ = laboratory value elevated at baseline to a clinically-significant degree**

Table 4
Numbers of Patients with Clinically-Significant Changes
in Hemoglobin, Hematocrit, or White Blood Cells

Test	Baseline Value	Baseline N	Time at which Clinically-Significantly Deviant Value was First Noted				
			3 months	6 months	9 months	12 months	24 months
Hemoglobin							
	11	1	-	11	-	-	-
	1	5	11	-	11	11	21
	WNL	5	11	-	-	11	31
	1	-	-	-	-	-	-
	11	-	-	-	-	-	-
Hematocrit							
	11	-	-	-	-	11	21
	1	3	-	-	-	-	11
	WNL	1	-	-	-	-	-
	1	-	-	-	-	-	-
	11	-	-	-	-	-	-
White Blood Cell Count							
	11	3	-	11	21	-	-
	1	19	41	21	11	71	41, 11
	WNL	15	41, 21	21	11	21, 11	21, 11
	1	1	-	-	-	-	11
	11	-	-	-	-	-	-
	U	5	11	11	11	11	11

- 11 = Laboratory value decreased at baseline to a clinically-significant degree
- 1 = laboratory value below normal range at baseline (but not to a clinically-significant degree)
- WNL = laboratory value within normal range at baseline
- 1 = laboratory value above normal range at baseline (but not to a clinically-significant degree)
- 11 = laboratory value elevated at baseline to a clinically-significant degree
- U = laboratory value unknown at baseline

Table 5
Numbers of Patients with Clinically-Significant Changes in Coagulation Factors

Test	Baseline Value	Baseline N	Time at which Clinically-Significantly Deviant Value was First Noted				
			3 months	6 months	9 months	12 months	24 months
Platelet Count							
		-	-	-	-	-	-
		-	-	-	-	-	-
	WNL	1	11	-	-	-	-
		-	-	-	-	-	-
		-	-	-	-	-	-
Prothrombin Time (PT)							
		-	-	-	-	-	-
		-	-	-	-	-	-
	WNL	-	-	-	-	-	-
		-	-	-	-	-	-
		-	-	-	-	-	-
Partial Thromboplastin Time (PTT)							
		-	-	-	-	11	-
		1	-	-	-	-	-
	WNL	1	11	-	-	-	-
		1	11	-	-	-	-
		-	-	-	-	-	-
	U	1	-	11	-	-	-

|| = Laboratory value decreased at baseline to a clinically-significant degree
 | = laboratory value below normal range at baseline (but not to a clinically-significant degree)
 WNL = laboratory value within normal range at baseline
 | = laboratory value above normal range at baseline (but not to a clinically-significant degree)
 || = laboratory value elevated at baseline to a clinically-significant degree
 U = laboratory value unknown at baseline

Table 6
Reversibility of Clinically-Significant Changes in Laboratory-Tests:
Numbers of Patients with Clinically-Significant Laboratory Changes whose
Values Returned to their Baseline Grade

Laboratory Test	Values Returned to Baseline Grade?	
	Yes	No or Unknown
SGOT	7	6
LDH	1	2
Alkaline Phosphatase	0	1
Total Bilirubin	3	4
Creatinine	1	1
Hemoglobin	0	4
Hematocrit	1	10
White Blood Cell Count	7	36
Platelet Count	1	0
PT	0	0
PTT	0	4

Reviewer's Conclusions:

Vital signs were not evaluated before, during, or exposure to Elmiron. Hence, possible effects of Elmiron on vital signs must come indirectly (e.g., through an analysis of adverse event data). Such an analysis is beyond the scope of this review. The most comprehensive treatment of the adverse event data may be found in the clinical/statistical review dated 1/31/96

Laboratory test data were missing on substantial percentages of patients in the physicians' usage program at all time points, and the program did not have a concurrent control group. Thus, the conclusions that can be drawn are limited. The database was largest at the three-month time point. On the one hand, no clear adverse trends emerged from these laboratory data. However, on the other hand, adverse effects of Elmiron on hepatic function, hematologic function, or coagulation indices cannot be excluded (at least in some patients).

2. Please perform a demographic subset analysis for safety (age, race, gender) for pivotal and open label physician's usage study databases.

Reviewer's Analysis:

Tables 7 and 8 describe the demographics of patients enrolled in the two placebo controlled studies (E001 and E002) and in the physicians' usage program. The vast majority of patients were female and white. Of the 2938 patients, about 23% were greater than 60 years of age.

Table 7
Demographics of Patients in Placebo-controlled Studies
(n=128)

women	123 (96%)
men or unknown	5 (4%)
≤ 60 years of age	101 (79%)
> 60 years of age or unknown	27 (21%)
white	126 (98%)
nonwhite or unknown	2 (2%)

Table 8
Demographics of Patients in the Physician's Usage Program
(n=2810)

women	2523 (90%)
men	287 (10%)
≤ 60 years of age	2155 (77%)
> 60 years of age	651 (23%)
unknown	4 (<1%)
white	2643 (94%)
nonwhite	70 (2%)
unknown	97 (3%)

The relatively low frequency of any specific adverse event decreases the likelihood that demographic factors that may influence the rate of that specific adverse event will be identified. In addition, demographic comparisons of the frequency of adverse events based on sex or race are limited in this database because the vast majority of the patients were women and the vast majority were white, and the comparator groups (men, non-whites) are correspondingly small. However, differences in the frequency of adverse events based on age are more likely to be detected because nearly one-fourth of the patients were greater than 60 years of age.

Given these limitations, Table 9 summarizes statistically-significant differences in the frequency of adverse events between demographic groups that were identified by the statistical review (review dated

07/09/96). Headache was more significantly more common in patients ≤ 60 years of age than in older patients, and was more common in women than in men. Alopecia was also more common in women than in men.

Table 9
Adverse Events with Different Frequencies in Different Demographic Groups
Physician's Usage Trial (n= 2810)

	≤ 60 years	> 60 years	p value	men	women	p value
Headache	3.6%	0.6%	< 0.001	0.35%	3.2%	0.006
Alopecia	—	—	—	0.7%	4.3%	0.003

Reviewer's Conclusions:

As this study did not have a concurrent control group, it is unclear whether the differential frequencies of headache and alopecia in the different demographic groups are real or spurious, related to Elmiron administration or not, or related to other factors (e.g., differential reporting frequencies).

3. *Please submit the case report forms (CRF) for the remaining 26 patients with serious adverse events as reported in appendix F in the June, 1995 Investigators Brochure. Also, please provide CRF's for patients reporting alopecia. Include line listings and an analysis of these events (i.e., number of patients, time of occurrence, resolution, treatment, concomitant medications).*

Case-Report Forms have been submitted as requested.

Reviewer's Analysis:

Serious Adverse Events:

Thirty-six (36) serious and/or unexpected clinical events were reported from the initiation of the Physician's Usage Program in 1986 through June 1995. These have already been reviewed (see section 3.4.3 and Appendix F of the Joint Medical-Statistical review dated 01/31/96), and will not be discussed further.

Alopecia:

Of the 2810 patients exposed to Elmiron in the physicians' usage program, 110 (3.9%) reported at least one event of alopecia. Of these 110 patients, alopecia was approximately equally distributed between patients greater than 60 years of age, and those ≤ 60 years of age. Women appeared to have a higher incidence than men, and non-whites appeared to have a higher incidence than whites. Signs of alopecia appeared as early as six days and as late as four years after initiation of Elmiron therapy. Fifty percent (50%) of the cases of alopecia occurred in the first three months of exposure to Elmiron, and 79% of all alopecia cases occurred within the first year. Of the patients reporting the onset of alopecia in the first three months, 56% experienced hair loss within 28 days. More than half of the patients who developed alopecia dropped out of the study for this adverse event ($57/110 = 51.8\%$). Fourteen women either began or were on treatment for hypothyroidism when they developed alopecia. Three patients had alopecia prior to Elmiron therapy.

Ninety-seven percent (97%) of the cases of alopecia were alopecia areata, limited to a single area on the scalp. Other forms of alopecia included alopecia universalis (n=3), alopecia totalis (n=1), and alopecia areata limited to the pubic hair (n=1).

Follow up was not available on all patients. In the 53 (48.2%) cases where follow-up information was available, hair loss was reversible upon discontinuation of Elmiron or a decrease in the Elmiron dose (usually from 300 mg to 200 mg/day). The time to complete resolution of alopecia ranged from 2 weeks to 1 year. One of four patients rechallenged with 300 mg/day of Elmiron had a recurrence of alopecia. Alopecia spontaneously resolve in nine patients who continued treatment at 300 mg/day.

Reviewer's Conclusions:

As noted in earlier reviews, alopecia is one of the most frequent adverse events associated with Elmiron therapy. Whether alopecia is caused by the drug or is related to other factors (e.g., underlying disease process) remains unclear, because this was an uncontrolled study.

4. *Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding pentosan polysulfate sodium. Please provide updated information as listed below:*

- a. *Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the current NDA amendment was submitted and any subsequent reactions will facilitate the review.*
- b. *Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.*
- c. *Provide details of any significant changes or findings, if any.*
- d. *Summarize worldwide experience on the safety of this drug.*
- e. *Please submit case report forms for any patients studied since the submission of the August 31, 1995, amendment, who died during treatment or withdrew from the study because of an adverse event.*

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Reviewer's Comments:

The sponsor submitted an updated tabulation of adverse events and discontinuations from the physicians' usage study.

Adverse Events: The original tabulation of adverse events from 1986 to December 31, 1994 (N=2504) has been updated to include the 2810 patients with data available as of February 29, 1996. I have sorted these adverse events by incidence, the results of which may be found in Appendix A.

Table 10
Most Frequent Adverse Events in the Physicians' Usage Study (n=2810)
Through February 29, 1996

Alopecia	110	3.91%
Diarrhea	106	3.77%
Nausea	104	3.7%
Headache	82	2.92%
Rash	71	2.53%
Dyspepsia	61	2.17%
Abdominal Pain	54	1.92%
Pain	54	1.92%
Dizziness	31	1.1%
Lack of Drug Effect	31	1.1%
Liver Function Test Abnormalities	29	1.03%
Asthenia	28	1.0%
Flatulence	23	0.82%
Pruritus	19	0.68%
Weight Gain	19	0.68%
Ecchymosis	18	0.64%
Paresthesia	18	0.64%
Anemia	17	0.6%
Arthralgia	17	0.6%
Vomiting	15	0.53%
Gastrointestinal Disorder	13	0.46%
Hematuria	13	0.46%
Insomnia	13	0.46%
Urinary Tract Infection	13	0.46%

Overall, the adverse event profile is similar to that outlined in the joint clinical/statistical review (date 01/31/96). Alopecia has the highest frequency (3.91%). Gastrointestinal disturbances are common

(e.g., diarrhea, nausea, dyspepsia, liver function test abnormalities, flatulence, vomiting, gastrointestinal disorder). Other dermal symptoms in addition to alopecia occur with a relatively high frequency (e.g., rash, pruritus). The relatively high frequency of ecchymosis (0.64%) also suggests that coagulation disorders also occur. Notably, "lack of drug effect" was also common (1.1%).

Discontinuations: To date, 130 patients have withdrawn from the physicians' usage program because of adverse events. For reference, these are listed in Appendix B.⁶ The continuation of Appendix B describes the demographics of the patients.⁷ Consistent with the composition of the patients enrolled in the program, most discontinuations were by white women. Of note, several adverse events that led to discontinuation were described as having a "probable" relationship to therapy with Elmiron. These included atrophic bilateral macular degeneration [patient breast carcinoma-stage II breast cancer (cystitis (bladder infection) ; elevated SGOT hair loss headache insomnia leukocytosis, lymphocytosis, and neutropenia signs and symptoms of mania and psychosis vaginitis (vaginal infection and vasodilation (hot flashes) and yeast infection]

World-wide exposure: As stated by the sponsor: supplies the active ingredient, pentosan polysulfate sodium (PPS), used in Baker Norton's oral Elmiron formulation for the treatment of interstitial cystitis." Worldwide patient exposure to pentosan polysulfate manufactured by is tabulated in the exposure table in Appendix C.

As stated by the sponsor: Pentosan polysulfate was first marketed in 1964 and since then has become available in numerous countries in both the tablet and capsule formulations at an average daily dose of 300 mg. Other than for treatment of interstitial cystitis, PPS is indicated for thrombosis prophylaxis and treatment, an anti-arteriosclerotic and treatment of thrombophlebitis. As of 12/95, over individual patient dosage forms have been marketed with an estimated patient exposure of

Reviewer's Recommendation:

The adverse events listed in the "Adverse Reactions" section of the labeling should be cross-referenced with the adverse events in Appendix A, for consistency. The more serious adverse events that led to discontinuations are problematic. It is difficult to exclude other possible causative factors (e.g., underlying disease, other illnesses, concomitant medications) to be able to attribute these adverse events to Elmiron. The world-wide exposure to Elmiron (estimated by the sponsor to be) is quite large.

5. Please devise a Patient Package Insert which we will review in conjunction with your response to the Pharmacokinetics and Clinical sections of this letter. Enclosed is a format guide to follow when developing this insert.

Baker Norton Pharmaceuticals, Inc. included a Patient Package Insert with this submission.

Reviewer's Comments and Recommendations:

⁶ In Appendix B, the First column is the Patient Identification. The second column is the adverse event as reported by the investigator. The third column is the time the adverse event occurred. The fourth column states the severity of the adverse event. The fifth column describes what treatment was needed. The last column provides the relationship to Elmiron.

⁷ In Appendix B (continued), the first column is the Patient Identification. The second column is the patient's age in years. The third column is the patient's sex. The fourth column is the patient's race. And the fifth column is the adverse event as reported by the investigator (a wider column to facilitate reading).

With some minor modifications, the Patient Package Insert will be adequate.

- 1) The following three items should be included as bullet items under the heading "Who should not take Elmiron?" (a) patients with liver problems, (b) patients who are allergic to Elmiron or to similar products such as certain blood thinners, and © patients with a history of heparin-induced thrombocytopenia.
- 2) The first heading under the heading "What are the possible side effects of Elmiron?" should be changed. Currently, it states the following:

"Possible side effects are hair loss, diarrhea, nausea, headache, rash, upset stomach, dizziness, and bruising."

This should be changed to read as follows:

"The most common side effects are hair loss, diarrhea, nausea, headache, rash, upset stomach, damage of the liver, dizziness, and bruising."

6. *Please provide the structural formula of the active ingredient of Hemoclar and say whether you think it is chemically identical to that of Elmiron.*

A laboratory evaluation at _____ was performed in 1993. Nine 1991 lots of bene (Elmiron) material and eight 1992 lots of _____ (Hemoclar) material were compared. These data suggest that compared to Elmiron, Hemoclar is less pure, slightly higher in molecular weight, and lower in impurities.

Reviewer's Assessment and Comments:

My own conclusions from these data, and an informal consult through a personal communication with a chemist (Dr. Eldon Leutzinger) were consistent with the sponsor's conclusions. Although Hemoclar appears to differ from Elmiron in these chemical parameters, the differences are small and the clinical significance of these differences, if any, is unknown. Other differences between these two drugs and the way they are used are likely to be of greater clinical significance. These include differences between the two drugs in manufacture, formulation, route of administration, dosage, duration of therapy, and patient characteristics (e.g., underlying disease process).

Biopharmaceutics/Pharmacokinetics:

In this submission, Baker Norton Pharmaceuticals, Inc. did provide raw data for some of the pharmacokinetics studies of interest. However, the sponsor was unable to provide adequate data to validate any of the assays that were used. Accordingly, as discussed in the Clinical Pharmacology and Biopharmaceutics review of this submission (draft dated 09/16/96) the application remains not approvable from the perspective of biopharmaceutics.

Labeling:

I have appended my mark-up of the sponsor's proposed labeling with this review. These mark-ups were then reviewed and edited by the Division Director (Dr. Patricia Love). Excluding details that were added at the request of the FDA and minor editorial changes, the sponsor's proposed labeling differs most from the FDA's version in the following areas:

Reviewer's Comments:

The Clinical Pharmacology and Biopharmaceutics reviewer (Dr. David Lee) evaluated these changes (draft review dated 09/16/96). Dr. Lee recommended the following:

Dr. Love edited my mark-up of the sponsor's proposed labeling, and the results are consistent with this recommendation from the biopharmaceutics reviewer.

2. Clinical Trials section:

The sponsor has added a sentence providing one-year efficacy results: "After 1 year, 346/598 (58%) patients continued to be improved by 1 or 2 categories on the pain/discomfort scale."

Reviewer's Recommendation:

The FDA's wording should remain without addition of the one year results. The data presented in the joint clinical/statistical review (dated 01/31/96) indicate that few additional patients benefit from Elmiron therapy if they had not yet responded after six months.

I have also edited the description of the physicians' usage study to a) give percentages as a fraction of the number of patients originally enrolled, not the number remaining at any time point; b) provide more balance; c) provide clarity (e.g., out of context the statement that "after six

months, the percent of patients who reported the first onset of pain relief was less than 1.5% of patients originally in the study" seems awkward and is hard to understand); d) give more emphasis to the fact that this was an open-label study without a concurrent control group, and; e) clarify the purpose of the current table titled "Pain Sores in Reference to Baseline in Open Label Physician's Usage Study.

My recommendations for wording follow (*in bold italics*)::

A second clinical trial, the physician's usage study, was a prospectively-designed retrospective analysis of 2499 patients who received open-label Elmiron 300 mg a day. Of the 2499 patients, 2220 were women, 254 were men, and 25 were of unknown sex. The patients had a mean age of 47 years and 23% were over 60 years of age. By three months, 1307 (52%) of the patients had dropped out or were ineligible for analysis. Overall, 1192 (48%) patients received Elmiron for three months; 892 (36%) received Elmiron for six months; and 598 (24%) received Elmiron for one year.

Patients had unblinded evaluations every three months for the patient's rating of overall change in pain in comparison to baseline and for the difference calculated in "pain/discomfort" scores. At baseline, pain/discomfort scores for the 2499 patients were severe or unbearable in 60%, moderate in 33%, and mild or none in 7% of patients. The extent of the patients' pain improvement is shown in Table 1.

At three months, 491/2499 (20%) of the patients originally in the study had pain/discomfort scores that improved by one or two categories. By six months, an additional 116/2499 (5%) of patients had improved pain sores. After six months, the percent of patients who reported the first onset of pain relief was less than 1.5% of the patients originally in the study (see Table 2).

Table 1: Pain Scores Compared to Baseline in the Open-Label Physician's Usage Study (N=2499)¹		
Efficacy Parameter	3 months²	6 months²
<i>Patient rating of overall change in pain (recollection of difference between current pain and baseline pain)³</i>	<i>n=1161 Median = 3 Mean = 3.44 CI: (3.37, 3.51)</i>	<i>n=724 Median= 4 Mean= 3.91 CI: (3.83, 3.99)</i>
<i>Change in pain/discomfort score (calculated difference in scores at the time point and baseline).⁴</i>	<i>n = 1440 Median=1 Mean=0.51 CI: (0.45, 0.57)</i>	<i>n=904 Median = 1 Mean= 0.66 CI: (0.61, 0.71)</i>

¹ Trial not designed to detect the onset of pain relief.

² CI = 95% confidence interval.

³ Six-point scale: 1=worse, 2=no better, 3=slightly improved, 4=moderately improved, 5=greatly improved, 6=symptoms gone.

⁴ Three-point scale: 1=none or mild, 2=moderate, 3=severe or unbearable.

<i>Table 2: Number (%) of Patients with New Relief of Pain/Discomfort in the Open-Label Physician's Usage Study (N=2499)</i>				
	<i>at 3 months² (n=1192)</i>		<i>at 6 months³ (n=892)</i>	
<i>Considering only the patients who continued treatment</i>	<i>491/1192</i>	<i>(41%)</i>	<i>116/892</i>	<i>(13%)</i>
<i>Considering all the patients originally enrolled in the study</i>	<i>491/2499</i>	<i>(20%)</i>	<i>116/2499</i>	<i>(5%)</i>

- ¹ *First-time Improvement in pain/discomfort score by 1 or 2 categories.*
² *Number (%) of patients with improvement of pain/discomfort score at three months when compared to baseline.*
³ *Number (%) of patients without pain/discomfort improvement at three months who had improvement at six months.*

3. Information for Patients:

The sponsor qualified a sentence that indicates that Elmiron's anticoagulant effect may increase bleeding times. The qualification indicates that in healthy volunteers prolongation did not occur at doses of up to four times the daily recommended dose.

Reviewer's Recommendation:

The FDA's original wording should remain without the sponsor's proposed qualification. Patients who are administered Elmiron chronically may respond differently than healthy volunteers who were administered the drug acutely.

4. Precautions: Pregnancy subsection:

The sponsor made changes to this section based on calculations normalized for body weight (instead of body surface area) and based on the low human bioavailability.

Reviewer's Comments:

Interspecies toxicity comparisons should be based on body surface area, not body weight. It is also inappropriate to adjust for low human bioavailability if the same adjustment hasn't also been made for low animal bioavailability.

Reviewer's Recommendation:

As discussed with two ad hoc Pharmacology/Toxicology reviewers (Drs. Laraine Meyers and David Bailey), the sponsor's proposals should be rejected. In addition, the following sentence should be changed:

The recommended language is as follows:

5. Dosage and Administration section:

Reviewer's Recommendation:

The FDA's original wording should remain without the sponsor's proposed unlimited extension of the duration of therapy. Elmiron appears to lose any effectiveness it may have over time. To some extent, this loss is due to attrition of patients who discontinue its use. The following are my calculations based on data in Tables 13a, 13b, and 13c (pages 40-41) of the joint clinical/statistical review (dated 01/31/96).

Number (%) of patients who improved by one or two categories on the pain/discomfort scales when treated with Elmiron:

- a) at six months: 508/2499 = 20.3%
- b) at nine months: 391/2499 = 15.6%
- c) at twelve months: 262/2499 = 10.5%

Phase 4:

With one exception in this submission, Norton Baker Pharmaceuticals, Inc. has committed to undertake and report on the requested phase 4 studies. That is, even though all the raw data were unavailable, the sponsor has not committed to performing additional studies to characterize fully the effects of pentosan polysulfate sodium on platelets, coagulation parameters, and clotting factors (phase-4 commitment #3). The following includes a verbatim transcription of the FDA's request (in italics) and the sponsor's response to this item:

FDA's request:

Please commit to undertake and report on the following phase 4 studies:....

3. *If the raw data on anticoagulation effects noted in your submitted articles [Jallad, "Final Study Report: IVX-N-101...", "Baker Norton Pharmaceuticals, Inc., May 17, 1994; and Losonczy, et al., "Effect of pentosan polysulfate...", "Seminars in Thrombosis and Hemostasis, 17(1991), 394] are not available, then commit to performing an additional study to fully characterize the effects of pentosan polysulfate sodium on platelets, coagulation measures, and clotting factors.*

Sponsor's response:

The raw data dealing with bleeding times, prothrombin times and partial prothrombin times are included in the Jallad Final Study Report, which is included as Reference 6 in Appendix 14. Information of other coagulation parameters are from the published article, Seminars in Thrombosis and Hemostasis, 17 (1991), 394, (included as Reference 7 in Appendix 14) and the raw data are not available.

Reviewer's Recommendation:

Given the inability to validate the sponsor's assays and the preliminary nature of the pharmacokinetics and pharmacodynamic data, the sponsor should not be released from this Phase 4 commitment to perform additional pharmacodynamic studies.

Note: The project manager, Susan Cusack, spoke with the sponsor on September 20th, regarding this Phase 4 commitment. The sponsor agreed to perform the additional pharmacodynamic studies.

Promotional Material:

As requested, three copies of the introductory promotional material were submitted to the FDA.

Reviewer's Recommendation:

The major problem with the promotional material is the summary of the physicians' usage study:

For example, one brochure (in Appendix 13 of this submission) states the following:

*in additional retrospective clinical studies:

-within 3 months: 41% of patients demonstrated improvement in bladder pain

-at 6 months: an additional 13.2% of patients showed improvement

-at 1 year: 58% of patients continued to be improved. *

As noted above in my comments on the labeling (see the "Clinical Trials" section and the "Dosage and Administration Section") this presentation of the data is unbalanced and misleading. Also see page 21 "Reviewer's Recommendations." Any such claims should always be balanced by noting the large number of drop-outs in the study, and by calculating the percentage of new "responders" using the total number of patients who enrolled in the physicians' usage program (n=2499) as the denominator.

Manufacturing Inspection:

Baker Norton Pharmaceuticals, Inc. acknowledged that approval is contingent upon satisfactory inspection of its manufacturing facilities for conformance with current good manufacturing practices (CGMP). An inspection was performed in December 1995 and the results were satisfactory. The results of the inspection are good for a year.

Assessment:

Because the clinical component of the approvable letter requested additional safety data and did not ask for additional efficacy information, efficacy was not evaluated for the purpose of this memorandum (except for purposes of labeling and review of the sponsor's proposed promotional materials). The issue of whether the retrospective, open-label physicians' usage study, which lacked a concurrent control group, provides adequate evidence of efficacy is beyond the scope of this review. Suffice it to say that no new safety issues were identified in the review of this submission.

The sponsor has responded to each of the items in the approvable letter. Satisfactory responses have been provided for all of the issues listed in the Clinical/Statistical section. The sponsor has agreed to all of the requested Phase 4 commitments. However, the sponsor has not provided a satisfactory response to the Biopharmaceutics/Pharmacokinetics issues identified in the approvable letter. Hence, from the perspective of Biopharmaceutics, the application remains non-approvable.

Action: Approvable

Outstanding Items:

1. Baker Norton Pharmaceuticals must submit revised draft labeling for the drug (including the Patient Package Insert—see pages 16-17 of this memorandum) that is identical to the enclosed labeling.
2. The introductory promotional material must be revised, both in concordance with the comments noted in this memorandum, and in concordance with recommendations of the Division of Drug Marketing, Advertising, and Communications (see page 21 of this memorandum).

Victor F.C. Raczkowski

Victor F.C. Raczkowski, M.D., M.S.

Deputy Director

Division of Medical Imaging and Radiopharmaceutical Drug Products

Adverse Events: By incidence
Physicians' Usage Study
Through 02/29/96
N=2810

ALOPECIA	110	3.91
DIARRHEA	106	3.77
NAUSEA	104	3.7
HEADACHE	82	2.92
RASH	71	2.53
DYSPEPSIA	61	2.17
ABDOMINAL PAIN	54	1.92
PAIN	54	1.92
DIZZINESS	31	1.1
LACK OF DRUG EFFECT	31	1.1
LIVER FUNCTION TESTS ABNOR	29	1.03
ASTHENIA	28	1
FLATULENCE	23	0.82
PRURITUS	19	0.68
WEIGHT GAIN	19	0.68
ECCHYMOSIS	18	0.64
PARESTHESIA	18	0.64
ANEMIA	17	0.6
ARTHRALGIA	17	0.6
VOMITING	15	0.53
GASTROINTESTINAL DISORDER	13	0.46
HEMATURIA	13	0.46
INSOMNIA	13	0.46
URINARY TRACT INFECTION	13	0.46
BACK PAIN	11	0.39
DEPRESSION	11	0.39
DYSURIA	11	0.39
HYPERTENSION	11	0.39
PHARYNGITIS	11	0.39
SWEATING	11	0.39
VAGINITIS	11	0.39
CYSTITIS	10	0.36
GAMMA GLUTAMYL TRANSPEPTI	10	0.36
MIGRAINE	10	0.36
RHINITIS	10	0.36
CHEST PAIN	9	0.32
EDEMA	9	0.32
NAUSEA AND VOMITING	9	0.32
SINUSITIS	9	0.32
CONSTIPATION	8	0.28
EPISTAXIS	8	0.28
LACTIC DEHYDROGENASE INCR	8	0.28
LEUKOPENIA	8	0.28
MOUTH ULCERATION	8	0.28
SGOT INCREASED	8	0.28
DRY MOUTH	7	0.25
FLU SYNDROME	7	0.25
HYPERTONIA	7	0.25
MYALGIA	7	0.25

Adverse Events: By incidence
Physicians' Usage Study
Through 02/29/96
N=2810

NERVOUSNESS	7	0.25
SGPT INCREASED	7	0.25
WEIGHT LOSS	7	0.25
ALLERGIC REACTION	6	0.21
AMBLYOPIA	6	0.21
BRONCHITIS	6	0.21
CONJUNCTIVITIS	6	0.21
ERUCTION	6	0.21
MALAISE	6	0.21
METRRORRHAGIA	6	0.21
PELVIC PAIN	6	0.21
PHOTOSENSITIVITY REACTION	6	0.21
SOMNOLENCE	6	0.21
THROMBOCYTOPENIA	6	0.21
URINARY FREQUENCY	6	0.21
VAGINAL MONILIASIS	6	0.21
ANOREXIA	5	0.18
DYSPNEA	5	0.18
GASTRITIS	5	0.18
HYPOCHROMIC ANEMIA	5	0.18
INFECTION	5	0.18
MENORRHAGIA	5	0.18
NAIL DISORDER	5	0.18
TACHYCARDIA	5	0.18
TASTE PERVERSION	5	0.18
URTICARIA	5	0.18
CARDIOVASCULAR DISORDER	4	0.14
COLITIS	4	0.14
CONFUSION	4	0.14
DEATH	4	0.14
DRY SKIN	4	0.14
DYSPHAGIA	4	0.14
FEVER	4	0.14
GUM HEMORRHAGE	4	0.14
MYOCARDIAL INFARCT	4	0.14
PERIPHERAL EDEMA	4	0.14
TINNITUS	4	0.14
URETHRAL PAIN	4	0.14
URINE ABNORMALITY	4	0.14
VESICULOBULLOUS RASH	4	0.14
ABNORMAL DREAMS	3	0.11
ACNE	3	0.11
ARTHRITIS	3	0.11
BILIRUBINEMIA	3	0.11
COUGH INCREASED	3	0.11
EAR DISORDER	3	0.11
ENDOMETRIAL DISORDER	3	0.11
ESOPHAGITIS	3	0.11
FACE EDEMA	3	0.11

Adverse Events: By incidence
Physicians' Usage Study
Through 02/29/96
N=2810

HAIR DISORDER	3	0.11
LACRIMATION DISORDER	3	0.11
LEUKOCYTOSIS	3	0.11
MACULOPAPULAR RASH	3	0.11
MASTITIS	3	0.11
MENSTRUAL DISORDER	3	0.11
PALPITATION	3	0.11
RECTAL HEMORRHAGE	3	0.11
TOOTH DISORDER	3	0.11
VASODILATATION	3	0.11
ALKALINE PHOSPHATASE INCRE	2	0.07
ANGINA PECTORIS	2	0.07
ARTHROSIS	2	0.07
ASTHMA	2	0.07
BREAST CARCINOMA	2	0.07
CHILLS	2	0.07
CHOLELITHIASIS	2	0.07
DEPERSONALIZATION	2	0.07
EOSINOPHILIA	2	0.07
EYE DISORDER	2	0.07
EYE HEMORRHAGE	2	0.07
GENERALIZED EDEMA	2	0.07
HIRSUTISM	2	0.07
HYPERCHOLESTEREMIA	2	0.07
HYPOMENORRHEA	2	0.07
HYPOTENSION	2	0.07
KERATOCONJUNCTIVITIS	2	0.07
LARYNGITIS	2	0.07
LYMPHADENOPATHY	2	0.07
LYMPHOCYTOSIS	2	0.07
PROCTITIS	2	0.07
PROTHROMBIN INCREASED	2	0.07
SKIN DISCOLORATION	2	0.07
STOMATITIS	2	0.07
THYROID DISORDER	2	0.07
TREMOR	2	0.07
UTERINE HEMORRHAGE	2	0.07
VERTIGO	2	0.07
ABDOMEN ENLARGED	1	0.04
ABNORMAL VISION	1	0.04
ABSCCESS	1	0.04
ACCIDENTAL INJURY	1	0.04
ACUTE KIDNEY FAILURE	1	0.04
AGGRAVATION REACTION	1	0.04
AGITATION	1	0.04
ALDOSTERONE INCREASED	1	0.04
AMENORRHEA	1	0.04
ANXIETY	1	0.04
BALANITIS	1	0.04

Adverse Events: By incidence
Physicians' Usage Study
Through 02/29/96
N=2810

BILIARY PAIN	1	0.04
BLADDER CALCULUS	1	0.04
BLOODY DIARRHEA	1	0.04
BODY ODOR	1	0.04
BRADYCARDIA	1	0.04
CARCINOMA	1	0.04
CARCINOMA OF LUNG	1	0.04
CATARACT SPECIFIED	1	0.04
CELLULITIS	1	0.04
CEREBROVASCULAR ACCIDENT	1	0.04
CHOLECYSTITIS	1	0.04
CORONARY ARTERY DISORDER	1	0.04
CREATINE PHOSPHOKINASE INC	1	0.04
CUSHINGS SYNDROME	1	0.04
DEAFNESS	1	0.04
DEEP THROMBOPHLEBITIS	1	0.04
DIPLOPIA	1	0.04
DRUG INTERACTION	1	0.04
DUODENAL ULCER	1	0.04
DYSMENORRHEA	1	0.04
EAR PAIN	1	0.04
ECZEMA	1	0.04
EMOTIONAL LABILITY	1	0.04
EPIDIDYMITIS	1	0.04
ERYTHROCYTES ABNORMAL	1	0.04
EUPHORIA	1	0.04
EXFOLIATIVE DERMATITIS	1	0.04
EYE PAIN	1	0.04
FACIAL PARALYSIS	1	0.04
FECAL INCONTINENCE	1	0.04
FEMALE LACTATION	1	0.04
FIBROCYSTIC BREAST	1	0.04
GASTROENTERITIS	1	0.04
GASTROINTESTINAL HEMORRHA	1	0.04
GENERALIZED EDEMA	1	0.04
GINGIVITIS	1	0.04
GLOSSITIS	1	0.04
GOITER	1	0.04
HEART ARREST	1	0.04
HEMORRHAGE	1	0.04
HEPATOMA	1	0.04
HERNIA	1	0.04
HERPES ZOSTER	1	0.04
HYPERGLYCEMIA	1	0.04
HYPERLIPEMIA	1	0.04
HYPERTENSION	1	0.04
HYPERURICEMIA	1	0.04
HYPOCHOLESTEREMIA	1	0.04
HYPOKALEMIA	1	0.04

Adverse Events: By incidence
Physicians' Usage Study
Through 02/29/96
N=2810

HYPOPHOSPHATEMIA	1	0.04
HYSTERIA	1	0.04
INCOORDINATION	1	0.04
INCREASED SALIVATION	1	0.04
INTESTINAL OBSTRUCTION	1	0.04
JOINT DISORDER	1	0.04
KIDNEY CALCULUS	1	0.04
LAB TEST ABNORMAL	1	0.04
LARGE INTESTINE PERFORATIO	1	0.04
LE SYNDROME	1	0.04
LEG CRAMPS	1	0.04
LEG CRAMPS	1	0.04
MANIC REACTION	1	0.04
MELENA	1	0.04
MYELOPROLIFERATIVE DISORDE	1	0.04
NECK RIGIDITY	1	0.04
NEPHRITIS	1	0.04
NEURALGIA	1	0.04
NEUROPATHY	1	0.04
NOCTURIA	1	0.04
OPTIC ATROPHY	1	0.04
OPTIC NEURITIS	1	0.04
OPTIC NEURITIS	1	0.04
OSTEOPOROSIS	1	0.04
OTITIS EXTERNA	1	0.04
PAPANICOLAU SMEAR SUSPICIO	1	0.04
PATHOLOGICAL FRACTURE	1	0.04
PEPTIC ULCER SYNDROME	1	0.04
PERIODONTAL ABSCESS	1	0.04
PERIPHERAL NEURITIS	1	0.04
PETECHIA	1	0.04
PHOTOPHOBIA	1	0.04
PLATELET ADHESIVENESS DECR	1	0.04
PNEUMONIA	1	0.04
PROLACTIN INCREASED	1	0.04
PROSTATIC CARCINOMA	1	0.04
PROSTATIC DISORDER	1	0.04
PSYCHOSIS	1	0.04
PSYCHOTIC DEPRESSION	1	0.04
PUSTULAR RASH	1	0.04
PYELONEPHRITIS	1	0.04
REACTIVATED DUODENAL ULCE	1	0.04
RETINAL ARTERY OCCLUSION	1	0.04
RETINAL DISORDER	1	0.04
RETINAL HEMORRHAGE	1	0.04
RETINAL VEIN THROMBOSIS	1	0.04
RHEUMATOID ARTHRITIS	1	0.04
SALPINGITIS	1	0.04
SCREAMING SYNDROME	1	0.04

Adverse Events: By incidence
Physicians' Usage Study
Through 02/29/96
N=2810

SEBORRHEA	1	0.04
SKIN BENIGN NEOPLASM	1	0.04
SKIN DISORDER	1	0.04
SLEEP DISORDER	1	0.04
SPLENOMEGALY	1	0.04
STOMACH ULCER	1	0.04
STOMACH ULCER HEMORRHAGE	1	0.04
SUBARACHNOID HEMORRHAGE	1	0.04
SUPRAVENTRICULAR TACHYCAR	1	0.04
SYNCOPE	1	0.04
TASTE LOSS	1	0.04
TENDINOUS CONTRACTURE	1	0.04
TENDON DISORDER	1	0.04
TENESMUS	1	0.04
TENOSYNOVITIS	1	0.04
THROMBOPLASTIN DECREASED	1	0.04
TOOTH CARIES	1	0.04
TOOTH DISCOLORATION	1	0.04
TWITCHING	1	0.04
ULCERATIVE COLITIS	1	0.04
URINARY RETENTION	1	0.04
UTERINE FIBROIDS ENLARGED	1	0.04
VAGINAL HEMORRHAGE	1	0.04
VASCULAR DISORDER	1	0.04
VASCULAR HEADACHE	1	0.04
VISUAL FIELD DEFECT	1	0.04
VOICE ALTERATION	1	0.04

Discontinuations
Physicians' Usage Study
N=2810

"ANT BITE" TYPE LESION ALL OV	3 MOS	MILD	BENADRYL 50 MG PO Q 6 HR	POSSIBLE
ABDO. PAIN (INTESTINAL CRAM	24 DAYS			POSSIBLE
ABDOMINAL CRAMPS	6 DAYS	MODERATE		POSSIBLE
ABNORMAL LIVER FUNCTION	48 MOS	MODERATE		POSSIBLE
ABNORMAL LIVER FUNCTION	4 MOS	MILD		POSSIBLE
ALLERGIC REACTION	0 DAYS			POSSIBLE
ALOPECIA - HAIRLOSS	0 DAYS			POSSIBLE
AMBLYOPIA	3 MOS			POSSIBLE
ANEMIA (LOW HEMATOCRIT, HE	57 DAYS	MODERATE		POSSIBLE
ARTHRALGIA	28 MOS	MODERATE		POSSIBLE
ATROPHIC BILATERAL MACULA	90 MOS	SEVERE		PROBABLE
BILIRUBINEMIA	20 MOS	MILD		POSSIBLE
BLADDER PAIN	8 DAYS	SEVERE	PT. WAS PUT ON XANAX & BENA	POSSIBLE
BLADDER PAIN	2 DAYS	MODERATE		POSSIBLE
BLOATING	15 DAYS	MODERATE	STOPPING ELMIRON	POSSIBLE
BLURRED VISION	71 DAYS	MODERATE		POSSIBLE
BREAST CARCINOMA - STAGE II	17 MOS	SEVERE	4 CYCLES OF CHEMOTHERAPY	PROBABLE
CARDIOVASCULAR DISORDER	15 MOS	SEVERE		POSSIBLE
CARDIOVASCULAR DISORDER (	63 MOS	SEVERE		POSSIBLE
COULD NOT SLEEP	14 DAYS	SEVERE		POSSIBLE
CYSTITIS (BLADDER INFECTION)	0 DAYS	SEVERE	WILL BE SEEING PHYSICIAN TO	PROBABLE
DECREASED PLATELET COUNT	38 MOS			POSSIBLE
DEPERSONAL	0 DAYS			
DEPRESSION	3 MOS	MODERATE		POSSIBLE
DERMATITIS	0 DAYS		REDUCED ELMIRON DOSAGE	POSSIBLE
DIARRHEA	31 DAYS	SEVERE		POSSIBLE
DIARRHEA	14 DAYS	MODERATE		POSSIBLE
DIARRHEA	28 DAYS	SEVERE	PT. BEING HOSPITALIZED IVK-P	POSSIBLE
DIARRHEA	2 DAYS	SEVERE		POSSIBLE
DIARRHEA	11 MOS	SEVERE	HOSP.	POSSIBLE
DIZZINESS	31 DAYS	SEVERE		POSSIBLE
DIZZINESS	32 DAYS	MILD		POSSIBLE
DOUBLE VISION (SPLIT)	71 DAYS	MODERATE		POSSIBLE
DYSPEPSIA	9 DAYS		ZANTAC & PROPULSID	
ELEVATED BLOOD PRESSURE	8 DAYS	MODERATE		POSSIBLE
ELEVATED GGTP	42 MOS	MILD		POSSIBLE
ELEVATED LIVER ENZYMES	19 MOS	MODERATE		POSSIBLE
ELEVATED LIVER ENZYMES ON	26 MOS	MILD	LIVER CT SCAN NORMAL ON 8/3	
ELEVATED SGOT	28 MOS			
ELEVATED SGOT	16 MOS			PROBABLE
ELEVATED SGPT	28 MOS			
EXTREME BLADDER BURNING .	14 DAYS	SEVERE	PT. IS TAKING PYRIDIUM 100 MG	POSSIBLE
FATIGUE	31 DAYS	SEVERE		POSSIBLE
FEELING HIGH	3 MOS	MODERATE		POSSIBLE
FEVER	28 DAYS	SEVERE	PT. BEING HOSPITALIZED IVK-P	POSSIBLE
FEVER	11 MOS	SEVERE	HOSP.	POSSIBLE
FOUL ODOR TO URINE	0 DAYS	SEVERE		POSSIBLE
GASTRIC INTESTINAL UPSET	5 DAYS	MODERATE	XANAX & CARAFATE FOR GASTI	POSSIBLE
GENERALIZED PRURITUS	5 MOS	MODERATE		POSSIBLE
HAIR LOSS	42 DAYS	MODERATE		PROBABLE
HAIR THINNING (ALOPECIA)	3 MOS	MILD	NO TREATMENT GIVEN.	POSSIBLE
HAIRLOSS	15 MOS	MILD	ROGAINE TO SCALP	POSSIBLE
HAIRLOSS	2 DAYS	SEVERE		POSSIBLE
HAIRLOSS	50 MOS	SEVERE	NO TREATMENT GIVEN PER DO	POSSIBLE
HEADACHE	31 DAYS	SEVERE		POSSIBLE
HEADACHE	0 DAYS	SEVERE	TYLENOL - EVERY DAY	POSSIBLE
HEADACHE	9 DAYS	MILD	TYLENOL	POSSIBLE
HEADACHE	90 MOS	SEVERE		PROBABLE
HEADACHE	3 MOS			POSSIBLE

HEADACHE	39 DAYS	SEVERE	TOOK TYLENOL & ADVIL - DID N	POSSIBLE
HEADACHE	19 DAYS	MODERATE	PT. TRYING OTHER THERAPY.	POSSIBLE
HEADACHE	3 MOS			POSSIBLE
HEADACHE	0 DAYS			POSSIBLE
HEADACHES	51 DAYS	SEVERE	VICODIN AT NIGHT, ADVIL 200 M	POSSIBLE
HOSPITALIZED FOR IRRITABLE	0 DAYS	SEVERE	HOSPITALIZED	POSSIBLE
HYPERTENSION (ELEVATED BL	2 DAYS	MODERATE		POSSIBLE
HYPOPHOSPHATAEMIA	28 DAYS	SEVERE	PT. BEING HOSPITALIZED IVK-P	POSSIBLE
I.C. SYMPTOMS WORSENER	61 MOS	SEVERE		POSSIBLE
INCREASE IN BURNING	35 DAYS			
INCREASED GGT	14 MOS	MODERATE		POSSIBLE
INCREASED GGTP	0 DAYS		REPEAT LAB TEST IN 2 WEEKS.	POSSIBLE
INCREASED LFTS	51 MOS	MODERATE		POSSIBLE
INDIGESTION	13 DAYS	MODERATE	MAALOX & ZANTAC	POSSIBLE
INFECTIONS	35 DAYS			
INSOMNIA	31 DAYS	SEVERE		PROBABLE
INSOMNIA (DIFFICULTY SLEEPIN	0 DAYS			POSSIBLE
ITCHING ON HANDS & CHEST	0 DAYS			POSSIBLE
KIDNEY INFECTION	53 DAYS	SEVERE	CIPRO - ANTIBIOTIC	POSSIBLE
LACK OF DRUG EFFECT	42 DAYS	SEVERE	INTRAVESICAL OF CROMOLYN S	POSSIBLE
LACK OF DRUG EFFECT (FREQU	0 DAYS			POSSIBLE
LACK OF EFFICACY (SYMPTOMS	2 DAYS	MODERATE		POSSIBLE
LACRIMATION (WATERY EYES)	3 MOS			POSSIBLE
LEUKOCYTOSIS	-79 DAYS		HEMATOLOGIST EVALUATION	PROBABLE
LOW WBC	24 MOS	MODERATE		POSSIBLE
LYMPHOCYTOSIS	-79 DAYS		HEMATOLOGIST EVALUATION	PROBABLE
MIGRAINE HEADACHE	14 DAYS	MODERATE	PT D/C'D ELMIRON FOR 7 DAYS	POSSIBLE
MUSCLE SPASMS (HYPERTONIA	28 DAYS	SEVERE	PT. BEING HOSPITALIZED IVK-P	POSSIBLE
MYALGIAS	28 MOS	MODERATE		POSSIBLE
NAILS BECAME THINNER	13 MOS	SEVERE		POSSIBLE
NAUSEA	10 DAYS	SEVERE	DISCONTINUED	POSSIBLE
NAUSEA	31 DAYS	SEVERE		POSSIBLE
NAUSEA	14 DAYS	MODERATE		POSSIBLE
NAUSEA	15 DAYS	MODERATE	STOPPING ELMIRON	POSSIBLE
NAUSEA	51 DAYS	SEVERE	VICODIN AT NIGHT, ADVIL 200 M	POSSIBLE
NAUSEA	24 DAYS			POSSIBLE
NAUSEA	11 MOS	SEVERE	HOSP.	POSSIBLE
NAUSEA	71 DAYS	MODERATE		POSSIBLE
NAUSEA	18 DAYS			POSSIBLE
NAUSEA	0 DAYS			POSSIBLE
NEUTROPENIA	-79 DAYS		HEMATOLOGIST EVALUATION	PROBABLE
PARESTHESIA	14 DAYS	SEVERE		POSSIBLE
PELVIC PAIN EXACERBATED	7 MOS	SEVERE	IMIPRAMINE	POSSIBLE
PEPTIC ULCER DISEASE	0 DAYS			POSSIBLE
PHOTO SENSITIVE (LIGHT SENSI	0 DAYS			POSSIBLE
RASH	0 DAYS			POSSIBLE
RASH IN FACE AND ALL OVER HI	71 DAYS	MODERATE		POSSIBLE
SEVERE DIARRHEA	10 DAYS	SEVERE	DISCONTINUED	POSSIBLE
SEVERE STOMACH PAIN	19 MOS	SEVERE		POSSIBLE
SIGNS AND SYMPTOMS OF MANI	8 MOS	SEVERE	SPECIALIZED PSYCHIATRIC TRE	PROBABLE
SIGNS AND SYMPTOMS OF PSY	8 MOS	SEVERE	SPECIALIZED PSYCHIATRIC TRE	PROBABLE
SLEEP DISORDER	2 DAYS	SEVERE		POSSIBLE
SMALL AMOUNT OF BLOOD IN M	0 DAYS		STOPPED ELMIRON & HEPARIN -	POSSIBLE
STABBING PAIN IN BLADDER	40 DAYS	MODERATE		POSSIBLE
STOMACH PROBLEMS	3 MOS	MODERATE		POSSIBLE
STROKE	0 DAYS			
TOTAL BILIRUBIN ELEVATED	5 MOS	MILD	NONE	POSSIBLE
TREMBLING	0 DAYS			POSSIBLE
UTERINE BLEEDING	0 DAYS			POSSIBLE

Discontinuations
Physicians' Usage Study
N=2810

VAGINAL BLEEDING (VAGINAL H	11 MOS			POSSIBLE
VAGINITIS (VAGINAL INFECTION),	0 DAYS	SEVERE	WILL BE SEEING PHYSICIAN TO	PROBABLE
VASODILATION (HOT FLASHES)	30 DAYS	SEVERE		PROBABLE
VISUAL FIELD DEFECT	0 DAYS			POSSIBLE
VOMITING	28 DAYS	SEVERE	PT. BEING HOSPITALIZED IVK-P	POSSIBLE
VOMITING	24 DAYS			POSSIBLE
VOMITING	11 MOS	SEVERE	HOSP.	POSSIBLE
WBC INC (LEUKOCYTOSIS)	28 DAYS	SEVERE	PT. BEING HOSPITALIZED IVK-P	POSSIBLE
WEIGHT INCREASE	44 DAYS	MODERATE	NONE RESOLVED SPONTANEOU	POSSIBLE
YEAST INF ECTION	20 DAYS	SEVERE	GARLIC TABLETS	PROBABLE
YEAST INFECTION	3 MOS	MODERATE		POSSIBLE
YEAST INFECTION	3 MOS	MODERATE		POSSIBLE

Discontinuations Demographics
Physicians' Usage Study
N=2810

68	FEMALE	WHITE	"ANT BITE" TYPE LESION ALL OVER BODY-DERMITITIS RASH
28	FEMALE	WHITE	ABDO. PAIN (INTESTINAL CRAMPING)
77	FEMALE	WHITE	ABDOMINAL CRAMPS
53	FEMALE	WHITE	ABNORMAL LIVER FUNCTION
40	FEMALE	WHITE	ABNORMAL LIVER FUNCTION
42	FEMALE	WHITE	ALLERGIC REACTION
73	FEMALE	WHITE	ALOPECIA - HAIRLOSS
27	FEMALE	WHITE	AMBLYOPIA
40	FEMALE	WHITE	ANEMIA (LOW HEMATOCRIT, HEMOGLOBIN AND RBC)
41	MALE	WHITE	ARTHRALGIA
50	FEMALE	WHITE	ATROPHIC BILATERAL MACULAR DEGENERATION
35	MALE	WHITE	BILIRUBINEMIA
51	FEMALE	WHITE	BLADDER PAIN
63	FEMALE	WHITE	BLADDER PAIN
40	MALE	WHITE	BLOATING
52	FEMALE	WHITE	BLURRED VISION
52	FEMALE	WHITE	BREAST CARCINOMA - STAGE II BREAST CANCER
67	MALE	WHITE	CARDIOVASCULAR DISORDER
59	MALE	WHITE	CARDIOVASCULAR DISORDER (DEATH)
31	FEMALE	WHITE	COULD NOT SLEEP
40	FEMALE	WHITE	CYSTITIS (BLADDER INFECTION)
44	MALE	WHITE	DECREASED PLATELET COUNT
44	FEMALE	WHITE	DEPERSONAL
40	FEMALE	WHITE	DEPRESSION
32	FEMALE	WHITE	DERMATITIS
34	FEMALE	WHITE	DIARRHEA
61	FEMALE	WHITE	DIARRHEA
39	FEMALE	WHITE	DIARRHEA
50	FEMALE	WHITE	DIARRHEA
34	FEMALE	WHITE	DIARRHEA
34	FEMALE	WHITE	DIZZINESS
52	FEMALE	WHITE	DIZZINESS
52	FEMALE	WHITE	DOUBLE VISION (SPLIT)
39	FEMALE	WHITE	DYSPEPSIA
81	FEMALE	WHITE	ELEVATED BLOOD PRESSURE
46	FEMALE	WHITE	ELEVATED GGTP
51	FEMALE	WHITE	ELEVATED LIVER ENZYMES
71	FEMALE	WHITE	ELEVATED LIVER ENZYMES ON 6/1/92
37	FEMALE	WHITE	ELEVATED SGOT
33	FEMALE	WHITE	ELEVATED SGOT
37	FEMALE	WHITE	ELEVATED SGPT
30	FEMALE	WHITE	EXTREME BLADDER BURNING - DYSURIA
34	FEMALE	WHITE	FATIGUE
25	FEMALE	HISPAN	FEELING HIGH
39	FEMALE	WHITE	FEVER
34	FEMALE	WHITE	FEVER
30	FEMALE	WHITE	FOUL ODOR TO URINE
60	FEMALE	WHITE	GASTRIC INTESTINAL UPSET
35	FEMALE	WHITE	GENERALIZED PRURITUS

Discontinuations Demographics
Physicians' Usage Study
N=2810

45	FEMALE	WHITE	HAIR LOSS
40	FEMALE	WHITE	HAIR THINNING (ALOPECIA)
38	FEMALE	WHITE	HAIRLOSS
50	FEMALE	WHITE	HAIRLOSS
70	FEMALE	WHITE	HAIRLOSS
34	FEMALE	WHITE	HEADACHE
37	FEMALE	WHITE	HEADACHE
32	FEMALE	WHITE	HEADACHE
50	FEMALE	WHITE	HEADACHE
27	FEMALE	WHITE	HEADACHE
36	FEMALE	WHITE	HEADACHE
52	FEMALE	WHITE	HEADACHE
47	FEMALE	WHITE	HEADACHE
41	FEMALE	WHITE	HEADACHE
36	FEMALE	WHITE	HEADACHES
75	FEMALE	WHITE	HOSPITALIZED FOR IRRITABLE BOWEL SYNDROME
63	FEMALE	WHITE	HYPERTENSION (ELEVATED BLOOD PRESSURE)
39	FEMALE	WHITE	HYPOPHOSPHATAEMIA
39	FEMALE	WHITE	I.C. SYMPTOMS WORSENER
33	FEMALE	WHITE	INCREASE IN BURNING
67	MALE	WHITE	INCREASED GGT
53	FEMALE	WHITE	INCREASED GGTP
45	FEMALE	WHITE	INCREASED LFT'S
38	FEMALE	WHITE	INDIGESTION
33	FEMALE	WHITE	INFECTIONS
40	FEMALE	WHITE	INSOMNIA
55	FEMALE	WHITE	INSOMNIA (DIFFICULTY SLEEPING)
43	FEMALE	ASIAN	ITCHING ON HANDS & CHEST
41	FEMALE	WHITE	KIDNEY INFECTION
39	FEMALE	WHITE	LACK OF DRUG EFFECT
31	FEMALE	WHITE	LACK OF DRUG EFFECT (FREQUENT URINATION INCREASED)
36	FEMALE	WHITE	LACK OF EFFICACY (SYMPTOMS WORSENER)
27	FEMALE	WHITE	LACRIMATION (WATERY EYES)
68	MALE	WHITE	LEUKOCYTOSIS
56	FEMALE	WHITE	LOW WBC
68	MALE	WHITE	LYMPHOCYTOSIS
47	FEMALE	WHITE	MIGRAINE HEADACHE
39	FEMALE	WHITE	MUSCLE SPASMS (HYPERTONIA)
41	MALE	WHITE	MYALGIAS
32	FEMALE	WHITE	NAILS BECAME THINNER
36	FEMALE	WHITE	NAUSEA
34	FEMALE	WHITE	NAUSEA
61	FEMALE	WHITE	NAUSEA
40	MALE	WHITE	NAUSEA
36	FEMALE	WHITE	NAUSEA
28	FEMALE	WHITE	NAUSEA
34	FEMALE	WHITE	NAUSEA
52	FEMALE	WHITE	NAUSEA
35	FEMALE	WHITE	NAUSEA

Discontinuations Demographics
Physicians' Usage Study
N=2810

41	FEMALE	WHITE	NAUSEA
68	MALE	WHITE	NEUTROPENIA
31	FEMALE	WHITE	PARESTHESIA
58	FEMALE	WHITE	PELVIC PAIN EXACERBATED
34	FEMALE	WHITE	PEPTIC ULCER DISEASE
27	FEMALE	WHITE	PHOTO SENSITIVE (LIGHT SENSITIVITY)
43	FEMALE	ASIAN	RASH
52	FEMALE	WHITE	RASH IN FACE AND ALL OVER HIVES
36	FEMALE	WHITE	SEVERE DIARRHEA
37	FEMALE	WHITE	SEVERE STOMACH PAIN
73	FEMALE	WHITE	SIGNS AND SYMPTOMS OF MANIA
73	FEMALE	WHITE	SIGNS AND SYMPTOMS OF PSYCHOSIS
50	FEMALE	WHITE	SLEEP DISORDER
28	FEMALE	WHITE	SMALL AMOUNT OF BLOOD IN MOUTH
50	FEMALE	WHITE	STABBING PAIN IN BLADDER
40	FEMALE	WHITE	STOMACH PROBLEMS
72	MALE	WHITE	STROKE
66	FEMALE	WHITE	TOTAL BILIRUBIN ELEVATED
43	FEMALE	ASIAN	TREMBLING
41	FEMALE	WHITE	UTERINE BLEEDING
27	FEMALE	WHITE	VAGINAL BLEEDING (VAGINAL HEMMORRHAGE)
40	FEMALE	WHITE	VAGINITIS (VAGINAL INFECTION)
40	FEMALE	WHITE	VASODILATION (HOT FLASHES)
27	FEMALE	WHITE	VISUAL FIELD DEFECT
39	FEMALE	WHITE	VOMITING
28	FEMALE	WHITE	VOMITING
34	FEMALE	WHITE	VOMITING
39	FEMALE	WHITE	WBC INC (LEUKOCYTOSIS)
32	FEMALE	WHITE	WEIGHT INCREASE
36	FEMALE	WHITE	YEAST INFECTION
40	FEMALE	WHITE	YEAST INFECTION
25	FEMALE	HISPAN	YEAST INFECTION

**Countries In Which Pentosan Polysulfate Produced
Are
Marketed For Oral Application**

EXPOSURE TABLE

Country	Manufacturer	Product	Approval	Dosage Form	Dosage/day	Indication	As of 12/95 Marketed Approval	Patients Exposed (estimate)**
Argentina		Merinox	1971	50 mg tab	300 mg	anti-arteriosclerotic	•	Total of all countries listed
Austria		Polyanion	1965	25 mg tab	150 mg	anti-arteriosclerotic	•	
Portugal		Fibroside	1965	25 mg tab	100 mg	anti-thrombotic		
Spain		Fibrocid	1966	25 mg tab	50 mg	anti-hyperlipemic		
South Africa		Tavan - SP54	1968	25 mg tab	150 mg	anti-thrombotic		
Hungary		SP54	1975	25 mg tab	150 mg	treatment of phlebitis		
Germany		SP54	1964	25 mg tab	300 mg	anti-thrombotic		
~~Canada~~		Elmiron	1993	100 mg cap	300 mg	treatment of IC		
Australia		Elmiron	1994	100 mg cap	300 mg	treatment of IC	•	
Italy		Fibrase	unknown	50 mg cap	300 mg	anti-thrombotic		
Spain		Plasmaclar	unknown	25 mg cap	105 mg	anti-arteriosclerotic		
Spain		Rulin	unknown	25 mg cap	25 mg	anti-hypertensive		

* In Canada, Argentina, Austria and Australia a total of  dosage forms have been marketed.

** As of 12/95, oral dosage forms were sold in the countries listed above. The dosage form contained an average of 50 mg pentosan polysulfate (25-100 mg). Based on an average dose of 300 mg/day, six dosage forms were used per patient daily. For an average patient on one year of therapy (average treatment course), each patient received 2190 oral dosage forms. Then  dosage forms were administered to patients.

DIV

ADD - 6 1005

BRIEF MEDICAL REVIEW

NDA: 20193
DRUG: ELMIRON
INDICATION: INTERSTITIAL CYSTITIS
SPONSOR: BAKER NORTON
SUBMITTED: 2 MARCH 1995
RECEIVED: 6 MARCH 1995
REVIEWED: 27 MARCH 1995
REVIEWER: WAYMACK

BACKGROUND:

Elmiron is an agent that is believed by the sponsor to be efficacious in the treatment of interstitial cystitis, an inflammatory disease of the bladder that results in chronic pain, frequency and urgency. The exact mechanism of action by which Elmiron is efficacious in the treatment of interstitial cystitis is unknown. Elmiron has been approved for use in Europe as an antithrombotic agent. Earlier this year, the drug was withdrawn from the French market for what are reported to be safety reasons. This agency has requested information from the French regarding the exact reasons for the withdrawal as well as the data that led to this action. This information is not as yet available.

This sponsor previously submitted an NDA to this division requesting approval for Elmiron for the treatment of interstitial cystitis. That NDA was not approved due to this division's opinion that the NDA failed to provide adequate evidence from two well controlled trials, demonstrating that Elmiron was safe and efficacious in the treatment of the disease. The specific problem was related to the efficacy data.

Two pivotal well controlled trials had been performed and submitted to support the NDA. These two studies were however flawed in that they had multiple investigators involved in both pivotal trials. The studies were also flawed in that six different efficacy endpoints were chosen, and those that demonstrated statistically significant improvement in one of the trials, failed to demonstrate improvement in the other. Additionally, there was no Bonferroni correction made to compensate for the fact that six different endpoints had been chosen. Finally it should be noted that when reviewing the data, it was determined that if the data from a single investigator (the champion of this therapy) was removed from the study, not only was statistical significance lost, but even the trend towards benefit was lost. These points are discussed in greater detail in prior reviews.

In part, because of the orphan status of this disease, this division with support from the division of biometrics, offered to accept the second of the sponsors' two pivotal trials, as evidence of efficacy. This would therefore result in the sponsor only requiring one additional study documenting efficacy, in order for an NDA to be granted.

The sponsor requested and was granted a meeting to discuss these points. At that meeting on 16 February 1995, the sponsor requested that Elmiron be granted immediate approval for use in patients with interstitial cystitis. In return they offered to perform phase IV studies to provide additional evidence of efficacy. The sponsor also stated that it would be impossible to perform phase III studies due to a lack of adequate numbers of patients and investigators. Finally the sponsor stated that thousands of patients had been treated with Elmiron, in a compassionate usage protocol and that this further proved efficacy for the drug.

The sponsor was offered the opportunity to submit the data from the compassionate usage protocol, to this division, in order that the data could be reviewed to see if it provided evidence of efficacy that might be relevant to granting the NDA. The sponsor has submitted that data along with their summary of the meeting on 16 February 1995.

The sponsor's summary of the 16 February 1995 meeting is significantly at variance with my recollection of the meeting. The most significant disagreement in that regards is the statement "There was common agreement between BNP and the FDA staff attending the meeting that Elmiron provides substantial benefit for a subset of IC patients and that there is a clear and urgent need for this drug in these patients." which appears in their meeting summary. This statement is not an accurate representation of the discussion at the meeting. While the sponsor did state their belief that Elmiron is effective, the FDA staff repeatedly stated the belief that there is insufficient data indicating substantial benefit from Elmiron for IC patients.

The sponsor's review of their compassionate usage data is summarized below.

A total of 1885 patients have been enrolled to receive Elmiron on a compassionate use basis since 1986. The number of patients entered per year since 1988 has ranged from 298 to 367. Of the patients entered to date, almost 300 patients have received the drug for at least two years. Among those who stop taking the medicine, it is noted that 47% failed to return to the clinic to have their prescription refilled following their initial receipt of the medication. The sponsor states that this rate of failing to refill the prescription was probably due to a lack of effectiveness in those patients, and that the drop out rate decreases after the second clinic visit.

A total of 175 patients stopped taking the medication due to adverse events. The most common adverse events were alopecia, rash, diarrhea and headaches.

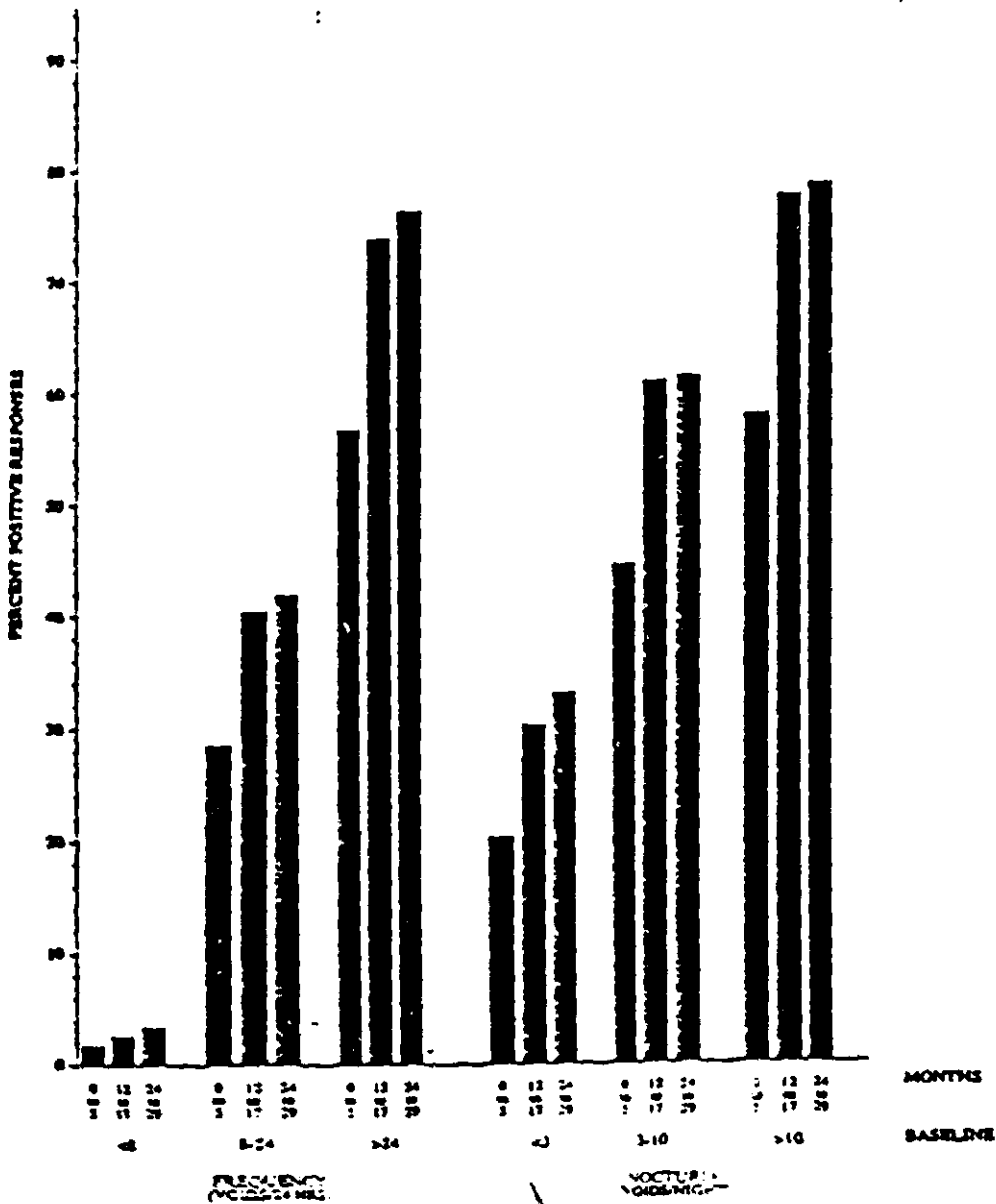
The sponsor states that the three most common reasons for patients discontinuing from the study are; remission of the disease due to the fact that the disease has a significant incidence of remissions and exacerbations, the cost of the drug, and the amount of paper work required of the urologists who prescribe the drug.

The sponsor has submitted a great deal of hard data to the FDA's biometrics division for analysis. They will be providing an extensive review of this data.

Briefly to summarize their findings, patients who initially had milder symptoms were more likely to claim benefit and to remain on the medication. These symptoms included frequency and pain.

The sponsor reports that improvement appeared to increase with time. As an example, at five months 13% of patients were graded as having scored "great improvements" in their overall condition. This was reported to increase to 33% at 60 to 90 months. This improvement with time was also apparent for the symptoms of urgency, frequency and pain.

The figure below documents the percent of improvement in frequency and nocturia as related to the initial severity of the disease and to the duration of therapy. As can be seen, improvement appears to increase during the initial 12 months of therapy, and to be greater as the number of initial voids per 24 hours or per night increases.



COMMENT:

The current submission's data is difficult to analyze due to a number of factors. These include the lack of a control group which makes any efficacy conclusions hazardous, and the fact that there was no a priori plan for long term monitoring of patients who stopped taking the drug.

Although the submitted data analysis would at first appear to suggest that patients did indeed improve after taking Elmiron, and that this improvement increased as the duration of therapy increased, there are three reasons why this conclusion may not be justified.

First, in the sponsor's two placebo controlled clinical trials, the response rate in the placebo group ranged from 11% to 46% depending on the parameter studied. Those numbers are not incompatible with the initial results reported from the compassionate usage patients described herein. As such, the null hypothesis may well apply.

Second, although the sponsor states that the response rate of the patients increases with increasing duration of therapy, this actually is not the case. This is due to the fact that a large percentage of patients dropped out of the study over time (approximately three quarters of the patients). One would have to assume that those patients who dropped out of the study were those that had failed to "respond" to the therapy while those who did respond remained on the medication. Since the sponsor elected to report the response rate over time using a percentage and with the denominator that was used to calculate this percentage being equal to the number of patients currently on the study medication rather than on the number who were initially on the medication; the increasing response rate was due to a decrease in the number of patients taking the drug who had failed to respond rather than to an increase in the number who responded. In other words, the numerator in the response rate equation did not change, but the denominator did (decreased), thereby increasing the percentage of patients who are stated to have responded to therapy. As such the sponsor's claim, that a greater percentage of patients responded as the duration of therapy increased, is severely misleading and is not justified by the data.

Finally, the fact that those patients who had the least severe disease were the most likely to respond to therapy, and since there is a large placebo effect with this disease, this further brings into question whether or not the drug has any real effect beyond that of a placebo.

ACTION:

Biometrics should be supplied with the hard data from this compassionate usage "study" so that they may attempt to discern if there is any real evidence of efficacy.

The sponsor should be informed that this division must disagree with the statement in their meeting summary which reads; "There was common agreement between BNP and the FDA staff attending the meeting that Elmiron provides substantial benefit for a subset of IC patients and that there is a clear and urgent need for this drug in these patients." We do not at present have confirmatory evidence that Elmiron provides any benefit to IC patients, and we so stated at the meeting on 16 February 1995.

cc IND FILES
DIV FILES
HFD-160 DIV DIR/DR LOVE
HFD-160 DIV MO/DR WAYMACK
HFD-160 DIV CSO/MS RHEE

29 August 1994

To: Dr. Love
From: Dr. Waymack
Re: NDA 20-193



As per your request, I have reviewed the Baker Norton NDA 20-193 for the purpose of evaluating whether or not the data from the two pivotal trials which were conducted to support the NDA, could be combined into a single large trial analysis. This request was the result of the flaws present in each individual trial analysis. Specifically, the numbers of patients in each trial (n=110 in trial E-001, and n= 148 in trial E-002) were insufficient to generate definitive proof of efficacy. These results are summarized below for intent to treat analysis which paralleled per protocol analysis, and had more significant p values due to the larger n values than did the per protocol values:

TRIAL E-001

	Placebo	Elmiron	p
Overall Improvement (Patient Impression)	13%	28%	.042
Bladder Pain Decrease	23%	42%	.005
Overall Improvement (Invest. Impression)	11%	26%	.039
Decrease in Urgency	39%	38%	.875
Bladder Pain Improvement	13%	26%	.068
Urgency Improvement	11%	22%	.087

TRIAL E-002

	Placebo	Elmiron	p
Overall Improvement (Patient Impression)	16%	32%	.022
Bladder Pain Decrease	46%	58%	.127
Overall Improvement (Invest. Impression)	15%	36%	.003
Decrease in Urgency	39%	57%	.035
Bladder Pain Improvement	18%	38%	.005
Urgency Improvement	18%	30%	.088

Although certain of these parameters would appear to be significant and to document efficacy, there were two major problems with these results. First, no Bonferroni correction was

performed on the alpha value (either a priori or post hoc), which was required to disprove the null hypothesis. Second, most of the significance in both trials was due to a single investigator who participated in both trials, Dr. Parsons. This is the same investigator whose preliminary studies, led to the IND on which this NDA is based.

The sponsor has previously been asked to address these two concerns. They have to date, not addressed the lack of a Bonferroni correction. They have reanalyzed the data from the E-002 trial, after excluding all the data from Dr. Parsons. When this was done, the lowest p value obtained was only .107, which was for the Overall Improvement (Investigator Impression). This raises a number of possible explanations for the significant p values obtained from the studies, other than the drug having an effect. These would include a different patient population at the site of Dr. Parsons investigations, a loss of blinding, some other form of bias, or a random statistical event.

Based on these problems, this division, with the concordance of Biometrics, has ruled that the two trials failed to provide adequate evidence of efficacy. This has led to a question as to whether one or two additional pivotal trials will be required prior to granting an NDA approval.

Since a minimum of two pivotal trials are required prior to granting an NDA approval, the only way the sponsor could gain approval, with only one additional pivotal trial, would be if the trials E-001 and E-002 could be combined to form a single pivotal trial which documents efficacy.

The two trials are not identical, and therefore the data could not easily be combined. Rather some form of meta analysis would probably be required. Although the feasibility and validity of such a meta analysis would best be addressed by Biometrics, a few points can be made.

The inclusion criteria for the two studies are not identical. They are however very similar and vary primarily in degree of severity of the symptoms the patient is experiencing. These differences include the following:

	E-001	E-002
Frequency	>10/day	8-24/day
Nocturia	>1/day	1-2/day
Voided Volume	<200 ml	50-200 ml
Bladder Capacity	<800 ml	350-1000 ml

Exclusion criteria and laboratory tests are essentially identical.

The dosage administration and randomization protocols are identical with the treated patients receiving 100 mg of Elmiron

t.i.d. and the controls a placebo. Efficacy parameters are the same. The method of quantitating these parameters although similar, are not usually identical. The pain and urgency scales are identical (see attached forms). However both the investigator's evaluation of overall improvement and the patient's follow-up questionnaire for overall improvement, although listing the same parameters (slight improvement, moderate improvement, etc) assign different percentages to these parameters (see attached forms).

From a medical clinical standpoint: I believe the inclusion criteria, exclusion criteria and safety parameters are so similar, that it would be reasonable to combine the data and simply use broader definitions of entry criteria to fit the combined protocol patient populations. I also believe that since the dosage and administration sections are essentially identical, you could reasonably combine the data. However, the differences in endpoint parameters are definitely not identical. As such there would be risk of obtaining a type I error by simply combining data. The best option may be a meta analysis, if Biometrics concurs. This analysis should be performed in two ways. One would be to combine the all data from both studies, while the second would be to combine all the data from both studies, excluding that obtained from Dr. Parsons.

To summarize, I remain convinced that due to a number of problems with the two trials, the NDA lacks sufficient and adequate data to support approving the NDA. At least one additional pivotal trial is indicated. Whether two trials are indicated should be determined by Biometrics deciding whether or not a meta analysis of the data obtained from trials E-001 and E-002, both with and without Dr. Parsons data, would generate valid conclusions.

Additionally, I strongly believe that any future pivotal trials should not include Dr. Parsons. This would eliminate the fear of any investigator specific effect, if efficacy were determined by the future trials.

CC: Dr. 8/20/77 - 2-195

HFD-160/Dickie

HFD-160/Smith/Turner

HFD-160/Smith/Turner

HFD-160/Rhee

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BRIEF MEDICAL REVIEW

NDA: 20-193
DRUG: ELMIRON
INDICATION: INTERSTITIAL CYSTITIS
SPONSOR: BAKER NORTON
RECEIVED: 17 FEB 1994
REVIEWED: 7 MARCH 1994
REVIEWER: J P WAYMACK

BACKGROUND: The sponsor has submitted a letter stating that they have finished an evaluation of Elmiron in normal healthy male volunteers. In this study, 32 males were randomized into one of five groups. These received either a placebo or one of four doses of elmiron. This preliminary two page report states that there were no major adverse events. A single patient in one of the treatment groups experienced a slight increase in his PT and PTT. The incidence of other adverse events appears to be equal between the treatment and placebo groups.

COMMENT: Although this data is encouraging, a full report will be required to determine if this study has truly documented safety at the dosages proposed for treating patients with interstitial cystitis. Such a report is apparently being prepared by the sponsor at this time. Until such a report is made available, this division should not concur with the sponsor's statement that the study documented safety.

ACTION: The sponsor should be thanked for the letter. The sponsor should also be informed that concurrence with the statement that the study provided convincing data that elmiron was found to be safe at the dosages suggested for treating interstitial cystitis, cannot be given until this division is provided with all of the data from the study.

cc NDA ARCH
HFD-160
HFD-160 DIV DIR/(DR LOVE)
HFD-160 DIV REVIEWER/(DR WAYMACK)
HFD-161 DIV CSO/(MS RHEE)

[Handwritten signatures and dates]
7 Mar 94
3/24/94

MEDICAL REVIEW

-7

NDA: 20-193
DRUG: Elmiron
INDICATION: Interstitial Cystitis
SPONSOR: Baker Norton Pharmaceuticals, Inc.
REVIEWER: J. Paul Waymack, MD, ScD
REVIEWED: 5 November

Reference is made to the NDA, amendment to a pending application, dated 7 July 1993 and received 9 July 1993, for Elmiron (pentosan polysulfate sodium).

The amendments dated 7 July 1993 attempt to address the five comments raised in our correspondence dated 27 January 1993. Below, I will respond to their responses. Their responses are listed as Comment, followed by my responses listed as Response.

Comment #1: The statistical analysis as presented in the statistical section (Section 6) of the original NDA addresses the comparison of treatment groups for all the pre-treatment variables collected in studies E-001 and E-002. Further examinations of comparability and patient disposition are discussed in this submission; please see Section I, Volume 1, p.3 for E-001 and Section II, Volume 2, p.1 for E-002. No baseline differences between the placebo and Elmiron groups were detected in either study.

An interim analysis was discussed in Section 6 of the original NDA submission: "..., after 50 patients were enrolled in the first study, an interim analysis was conducted to help determine the total number of patients that would be needed for a valid study. The number of patients planned for the second study was based on the results of the first study."

The results of this analysis did not change the performance of the study and were not divulged to any participant. There were no stopping rules associated with the analysis and the study continued until approximately the correct number of patients had completed the study.

Your comment is further addressed in the Introduction to the study analyses in Volume I, p. 1 of this submission.

Response #1:

This analysis establishes to my satisfaction that there were no identifiable baseline differences between the test and control

groups with respect to pertinent variables.

We should continue to request that statistical significance be set at 0.048 for the E001 study due to the interim analysis. Their response, while objecting to this reduction in the required p value, does use the adverb "only" to describe the miniscule but important change. I would therefore not anticipate that the change will have any significant effect on the outcome of the analysis of their data, and they should not be allowed to object to strenuously after they have elected to utilize that adverb. I do however, believe that the change is appropriate from a statistical standpoint.

Comment 1a: All patients studied in protocols E-001 and E-002 had the clinical diagnosis of interstitial cystitis.

We interpreted the "per protocol" analysis to include patients who met the strict eligibility requirements. These criteria define the target population of evaluable patients. Please refer to the Introduction, Volume 1, p.2 for a table describing each of the prestudy criteria used in this analysis. The results of this analysis demonstrate that Elmiron is an effective oral therapy for interstitial cystitis. (E-001: Section I, Volume 1, p. 7; E-002: Section II, Volume 1, p.5).

Response 1a:

Their comment failed to fully address the request made by this division in our correspondence dated 27 January 1993. Specifically, it is not clear whether or not all patients entered into the study were having symptoms of pain at the time of entry. I recognize that the presence of pain is listed as a requirement for entry into the study, however that this was indeed true of all patients is not clear from the documents they have supplied the FDA. They should either confirm that all patients did have symptoms of pain at the time of entry into the study, or provide the requested analysis of patients entered into the study, exclusive of those not having symptoms of pain at the time of entry.

Their statement that, "The results of this analysis demonstrate that Elmiron is an effective oral therapy for interstitial cystitis" I cannot concur with at present.

Comment 1b: This endpoint analysis as presented in the statistical section of the original NDA (Section 6) is an intent to treat analysis with the last available on study result brought forward for dropouts. The response analysis of the final overall evaluations also includes dropouts with the assumption that the outcome was rated as no improvement (i.e., including all randomized patients taking at least 1 dose of medication).

We have conducted intent to treat analyses that include all

randomized patients. For each of the monthly visits, an analysis of patients with reported results at that visit was performed. In addition, an analysis of endpoint data with last observation for patients with no follow-up. The results of these analyses can be found in the summary for each of the studies, (E-001: Section I, Volume 1, p.6; E-002: Section II, Volume 2, p.4); the statistical and clinical effectiveness of Elmiron has been confirmed.

Response 1b:

The "intent to treat" analysis in Section I, Volume 1, p.6 for E-001 and Section II, Volume 2, p.4 is noted and appears in order. Again, I am not convinced at this time that the statement in their response "the statistical and clinical effectiveness of Elmiron has been confirmed" is justified at this time.

Comment 1c:

The response rates of the evaluable (EVAL) patients are similar to those seen in the "intent to treat" (ITT) patients. A reduction in power results in lower statistical significance for evaluable patients. The following table presents overall improvement rates for investigator and patient evaluations. Detailed tables supporting this conclusion can be found in Section II, Volume 2, pp. 33 and 34 for E-002.

(Table not shown)

Response 1c:

I accept that the "per protocol and "intent to treat" analyses are similar.

Comment 1d:

A subgroup evaluation was conducted to identify populations in which the drug product may be especially effective. The primary response variable was overall improvement as rated by the investigator and by the patient at termination. Univariate and multivariate analyses were conducted to identify prestudy characteristics associated with effectiveness.

The variables examined were age, baseline symptoms including urinary frequency, urgency, nocturia, average voided volume, pain, duration of disease, and baseline cystoscopic findings including time since cystoscopic exam, bladder capacity, postcystoscopic bloody drainage, presence and severity of fissures, linear scars, glomerulations and petechial hemorrhages.

Baseline disease status was associated with an improved response to Elmiron. In particular, an improved response to Elmiron was demonstrated in those patients with mild to moderate disease as evidenced by bladder capacity findings of mild to moderate bloody

drainage.

There were no prognostic variables predictive of a placebo response.

A complete description of this subgroup evaluation can be found in Section III, Volume 2, p. 217 and the accompanying statistical presentation is located in Section III, Volume 2, p. 220.

Response 1d:

The data analysis presented appears to document that Elmiron may yield a more favorable result in patients who are in the early phases of the disease process. This statement is based on the assumption that Elmiron does have efficacy in the treatment of IC. Again, I am not yet ready to accept this conclusion.

Comment 2:

In the evaluation of the key parameters of response, overall improvement of symptoms is statistically significant for investigator and patient. For the disease parameters reported monthly, increases in response rates are seen through Month 2 (E-001: Section 1, Volume 1, pp. 29-33).

The data from E-002 showed continued increases in response rates through Month 3 with significant treatment group differences for pain, urgency and volume/void (E-002: Section II, Volume 2, p. 34). The histogram below illustrates increasing response in the analog pain scale over time, relative to placebo.

(Histogram not shown)

We will be happy to discuss specific labelling regarding the rate of symptom relief and the course of therapy required to achieve a therapeutic response. Our clinical consultants indicate that different disease and symptomatic parameters respond at different rates. For instance, the actual changes in bladder function may require several months before a successful therapy establishes a prolonged and maintained improvement profile. This may be in contrast to acute symptomatic changes. We believe that the continuous long term response to this oral therapy is critical to these patients.

Response 2:

I accept that the data presented on page 34, Section II, Volume 2, establishes that 6 to 8 weeks of Elmiron therapy may be required to achieve a beneficial result, again assuming Elmiron is efficacious.

Comment 3:

We agree that in the study of a multifactorial and

pathophysiologically complex disease such as interstitial cystitis it may be difficult to achieve center to center homogeneity. However, there are at least two investigators in each study in which the superiority of Elmiron over placebo is demonstrated. Placebo appeared to be favored over Elmiron when there was limited sample size of an individual investigator. Individual investigator results are illustrated in the graph on the next page, showing the differences in the response rates for the overall evaluations between treatments.

Although some center to center variations are seen, these do not influence the overall conclusion that Elmiron was significantly superior to placebo in both studies. A complete discussion and analysis of investigator interactions are provided as Section IV of this Amendment (Volume 3, pp. 1-31).

(Figure not shown)

Response 3:

I must first disagree with the statement that there are at least two investigators in each study who demonstrated superiority of Elmiron over placebo. When one uses a Bonferroni correction to compensate for the multiple parameters studied, the number of investigators demonstrating statistical significance is only one per study. Indeed, in the re-analysis of the data, the applicant failed to address the issue of multiple comparisons. If approval could be granted based on any of one of the applicant's six primary parameters, it is my opinion, that the significance level of each independent test will have to be adjusted to maintain the integrity of the overall significance level of the trial, such as the Bonferroni previously mentioned.

The lack of independence of the two trials remains worrisome. Trial E-001 had three investigators who participated in trial E-002. These investigators made up 75% (82/110) of the patients enrolled in trial E-001 and 57% of the patients enrolled in trial E-002. The two small centers which participated in trial E-001, but not in E-002, enrolled only 14 patients and thus cannot undergo an efficacy analysis by themselves.

Similar problems exist for protocol E-002. In addition, this trial has a serious interaction problem, where the significance observed was highly influenced by investigator 1. When investigator 1 is excluded, the direction of treatment effect, although still favoring Elmiron, does not even come close to reaching statistical significance.

I therefore continue to remain concerned with the lack of an adequate number of study sites and patients. I believe that the applicant has failed to provide two independent, adequate and well controlled trials substantiating the claim that 3 months on 100 mg of Elmiron, t.i.d., is efficacious in the treatment of interstitial cystitis.

I would be willing to accept the results of study E-002 as supportive evidence for the applicant's efficacy claim. However, a pivotal trial which uses investigators who did not participate in E-001 or E-002, and which specifies in the protocol a single primary efficacy parameter, or a plan which utilizes a multiple comparisons adjustment, will be required to demonstrate efficacy to my satisfaction.

Comment 4:

Our consulting investigators have indicated that a placebo withdrawal design for patients who have responded to Elmiron would be unacceptable, perhaps unethical. We shall be happy to discuss other postmarketing study designs such as suggested in Section VII, Volume 3, p. 157.

We have prepared a clinical efficacy summary of our compassionate use program containing information on 1885 patients treatment courses, treated for a period up to 7 years, by 702 physicians. An evaluation of these data (Section V, Volume 3, p. 32) indicates improvement of interstitial cystitis symptoms with time on drug.

Response 4:

I well aware that with any placebo withdrawal study, some patients will suffer a recurrence of their symptoms, BUT only if the test drug is efficacious. That fact has not yet been established for Elmiron. The logical extrapolation to their argument would be to state that one should never do a randomized, placebo controlled trial for a new product since if it works, half the patients would not do as well as the half in the test product group. Unfortunately, the efficacy of new products can only be established by having the half of the patients assigned to the placebo group, in either a placebo controlled or placebo withdrawal study, have an inferior outcome to the test product group.

Since their investigators are reluctant to perform this study, the use of the new pivotal study mentioned in Response 3 should suffice for demonstrating efficacy. Such a demonstration would render the placebo withdrawal study redundant.

Comment 5:

A summary of the Human Pharmacokinetics and Bioavailability Section is found in Section VI, Volume 3, p. 148. These studies involved intravenous, oral, and subcutaneous routes of administration of Elmiron (primarily single dose) and focused on the absorption, metabolism and elimination of the drug in healthy volunteers. Only limited pharmacokinetic data are available in patients with interstitial cystitis.

It is our intention to continue a post marketing Elmiron clinical

pharmacology program, evaluating: effects of food and pharmacokinetics in special populations (eg. elderly).

Response 5:

I concur with the other FDA reviewers of this NDA, that it is to be stressed that the to be marketed formulation for Elmiron be utilized for the conduct of the new clinical study (Titled: Urinary Concentration-Controlled Trial of Elmiron) in order to avoid a bioequivalence issue between a clinical formulation and the to be marketed formulation.

cc NDA ARCH
HFD-160
HFC-130
HFD-160/DIVDIR, Dr. P. Love
HFD-160/PRIMARY REVIEWER (Dr. P. Waymack)
HFD-160/CSO (Ms. Rhee)
HFD-713/Turney

Paul Waymack
9 Nov 1993

MEDICAL OFFICER'S REVIEW.

NDA 20-193
Original NDA

Submitted	6-11-1991
Received	6-19-1991
Assigned	6-26-1991
Completed	12-04-1991

SPONSOR:

Baker Cummins
Pharmaceuticals, Inc.,
8800 Northwest 36th Street
Miami, Florida 33178

NOTE: The clinical development of Elmiron was sponsored initially by under IND Later it was transferred to and finally transferred again on February 28, 1991 to the current sponsor: Baker Cummins Pharmaceuticals, Inc., who are submitting protocols E-001 and E-002 under NDA 20-193.

NAME OF DRUG:

Trade: Elmiron
Generic: Pentosan polysulfate sodium.

CLASSIFICATION:

1 CH

DOSAGE FORM:

Capsules 100 mg.

ROUTE OF ADMINISTRATION:

Oral

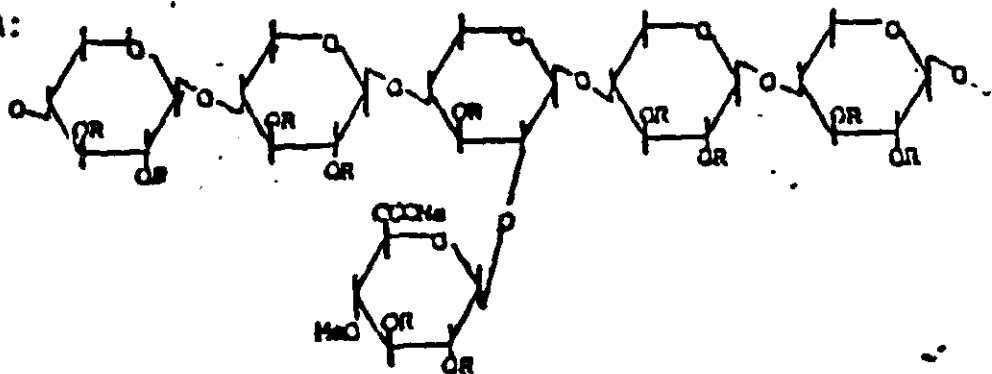
PROPOSED INDICATION:

For the treatment of symptoms of Interstitial cystitis.

PHARMACOLOGIC CATEGORY OF THIS DRUG:

Elmiron (pentosan polysulfate sodium) is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative which chemically and structurally resembles glycosaminoglycans. It is a white odorless powder, slightly hygroscopic and soluble in water to 50% at pH 6.

STRUCTURAL FORMULA:



MOLECULAR FORMULA:

$[C_5H_6O_4(SO_3Na)_2]_n$, where $n=17$

MANUFACTURING CONTROLS:
See Chemistry Review.

CLINICAL PHARMACOLOGY:

The Clinical Pharmacology of Elmiron is described in this submission as follows:

It has been suggested, that in patients with interstitial cystitis, the bladder has areas which are denuded of the glycosaminoglycans layer. Therefore, a proposed mechanism of action of Elmiron in this disease is that it binds to the transitional epithelium of the bladder and coats the denuded areas. Elmiron binds water very strongly thereby restoring the normal barrier between the epithelium of the bladder and the urine which is thought to be irritating to the denuded areas.

PHARMACODYNAMICS-PHARMACOKINETICS-BIOAVAILABILITY:

NOTE: The following discussion concerning Pharmacodynamics, Pharmacokinetics and Bioavailability has been excerpted from the sponsor's submission. Further evaluation will be found in the Biopharmaceutical review.

The distribution, metabolism, and elimination of Elmiron by using I-25 labeled drug has been shown, according to the sponsor, to be similar to that of heparin. In human volunteers subjects Elmiron was rapidly cleared from the plasma. It is stated that the liver and spleen are the major sites of desulphation and that depolymerization occurs in the kidneys. These end substances were found in urine post-injection.

The half-life of Elmiron administered intravenously to normal human volunteers and measured by a competitive binding assay was estimated as 22 minutes at a dose of 10 mg and 55 minutes at a dose of 100 mg.

Using tritiated Elmiron given orally to normal volunteers, it was shown that 40 to 60% of the radioactivity was absorbed, and it was calculated that 11% of the dose was excreted in the urine and 78% in the feces. This data indicated that about 3% of the Elmiron dose appeared in the urine as unchanged compound resulting in a concentration of Elmiron of up to 11 ug/ml in the urine 2 to 6 hours after administration"

The sponsor attached to this submission in Section Human Pharmacokinetic and Bioavailability Summaries the discussion of five studies, classified as Study 6-1, 6.2, 6.3, 6.4, and 6.5. These studies performed in Germany and England are reproduced in this reviewed volume.

Study 6-1: "Pentosan polysulfate (Elmiron): pharmacokinetics and effects on the urinary inhibition of crystal growth". Fellstrom B, et al., published in Darmstadt, W. Germany, 1987.

Pentosan polysulfate sodium (PPS) levels in plasma and urine were measured in eight male volunteers after intravenous and oral doses of PPS.

The kinetic parameters were as follows:

Distribution half-life.....	24.5 + 4.4 min
Elimination half-life.....	24.1 + 10.8 hr
Steady state distribution volume.....	0.67+ 0.68 l/kg
Plasma clearance.....	49.9 + 6.6 ml/min
Renal clearance.....	4.2 + 1.2 ml/min

The urinary excretion of PPS after 40 mg IV dose was 3.32 + 0.8 mg/24 h. After 400 mg of PPS orally, the urinary excretion was 230+94 ug/24 h after a single dose and 210 +90 ug/24 h after 3 weeks of daily dosing.

At this steady state with oral administration, plasma levels ranged from 0.02 to 0.05 ug/ml. Bioavailability of PPS was estimated to be 0.5-1% using the plasma or urine values of the oral and IV administration.

Study 6-2. "Sodium pentosan polysulfate: A pharmacokinetic study in man after oral administration". Greenslade D. et al.. Report from North Yorkshire, England, July 1983. Not published

In this report the absorption and elimination of radioactivity of PPS was measured in 3 male volunteers after a single dose of ³H-sodium pentosan polysulfate (tritiated PPS) at a dose of 2, 5, or 10 mg/kg of body weight. Serial samples of Blood, urine, and feces were collected at the following intervals post-dose:
Blood at 0, 0.25, 0.5, 1, 1.5, 2, 3, 6, 8, 12, 24, 48, 72, 96 and 120 hrs.
Urine was collected at each 2-hr interval for the first 14 hrs after dosing, from 14 to 24 hrs, and then during each 24 hrs. up to 120 hours.
Feces were collected during each 24 hr period up to 120 hrs.
The 3 subjects received 150, 315 or 693 mg of tritiated PPS orally. No side effects were observed or reported.

The authors gave the following data: "A mean of 83.7 + 11.6% of the administered radioactivity was recovered in the urine and feces during the 120 hour collection period. The majority of the radioactivity, 87% in 2 volunteers and 67% in the volunteer who received the lowest dose, was recovered in the feces. About 3.5% of the recovered radioactivity was from the urine at each dose level. Most of the radioactivity was recovered within 24 hrs in the urine, and within 72 hours in the feces".

Study 6-3: "Absorption, distribution, and excretion of ³H SP54 after parenteral and oral application (sic.) in eight healthy male volunteers". Kummer M. Kunz et al.. Report from Munich, West Germany. Not published. (1987).

Tritiated pentosan polysulfate sodium (PPS) was administered to 8 male volunteers in this two-way crossover study. PPS was administered IV (75mg) or PO (150 mg) and its absorption, distribution and excretion were studied during 7 day hospitalization after each administration of labeled drug.

According to the investigators, after a 150 mg oral dose of tritiated PPS, maximum plasma levels of radioactivity ranged from 0.17 to 0.45 ug equiv/ml (mean 0.3) reached in a range of 1 to 48 hours (mean 14). Total body clearance ranged from 66 to 625 ml/min (mean 191). About 27% of the parenteral dose and 11% of the oral dose of tritiated PPS were excreted in the urine up to 144 hours post-dosing. Absorption was calculated to be 40% of the oral dose given. Four percent of the parenteral dose and 78% of the oral dose were accounted for in the feces. Independent of the route of administration, 20 to 30% of the excreted radioactivity was found to be 6% (IV) and 3% (PO) of the given dose as unchanged PPS, providing up to 12 ug/ml PPS in the urine during the first 2 to 6 hours post-dose. The authors concluded that: "The results of these studies indicate that PPS reaches the urine unmetabolized in sufficient amounts to be effective in interstitial cystitis".

Study 6-4: "Metabolism of sodium pentosanpolysulfate in man-catabolism of iodinated derivatives". McGregor et al. Published in Edinburgh, U.K. (1984)

In this study the metabolism of an iodinated derivative of sodium pentosan polysulfate (PPS) as well as unlabeled PPS was studied by intravenous and subcutaneous injection in 5 healthy volunteers. Blood and urine samples were obtained at various times after injection.

At IV dose levels of 0.1, 1, and 7 mg, the radioactivity was cleared from the blood with a half life of 13 to 18 minutes. At the 50 mg IV dose the half life was 45 minutes. Radioactivity was detected at 5 minutes after the 50 mg SC injection and reached its peak level at 80 minutes

In this study it is also described that radioactivity was detectable in urine within 1 hour of IV injection. The recovery of radioactivity in the urine during the 24 hours following both IV and SC injection averaged 31% of the administered dose and was independent of the dose of unlabeled PPS. The major portion of the label was localized in the liver and spleen.

Study 6-5: "Metabolism of sodium pentosan polysulfate in man measured by a new competitive binding assay for sulphated polysaccharides. Comparison with effects upon anticoagulant activity, lipolysis, and platelet alpha-granule proteins". I. R. MacGregor et al..St. Bartholomew's Hospital, London U.K. Published.(1985)

For this study PPS was administered to each of three human volunteers at weekly intervals at doses of 0.1, 1, 10, and 100 mg IV and 100 mg SC. Blood samples were obtained before injection and at 5, 10, 20, 40, 80, 160, and 320 minutes following IV injection, or at 30, 60, 120, 180, 300, and 480 minutes after SC injection.

The half life of PPS in the circulation had a mean value of 7, 22, and 55 minutes after IV injection of 1, 10, and 100 mg respectively. PPS in circulation could not be detected after 0.1 mg PPS IV. The authors concluded that "the newly developed competitive binding assay, which does not measure PPS which has been inactivated by desulphation, provides a more sensitive means than conventional bioassays for the determination of PPS plasma concentration".

The sponsor states that as four of the five above studies have used radioisotopic methods alone for determining PPS levels the data from these studies could not contribute to the determination of the dose selection, or the optimal use of Elmiron. The clinical studies were based on the information available from the clinical use of Elmiron over the past 15 to 20 years in other indications for which it is approved in other countries, and some information from the experimental use over approximately 5 years for interstitial cystitis in the U.S. The total daily doses used were 300 to 400 mg without clinical difference in efficacy between 300 and 400 mg. "Based on the results of these earlier studies 300 mg per day was chosen for the clinical studies which form the basic support for the present application"

In three of the studies described above where oral Elmiron was used at different doses, bioavailability was estimated to range from 0.5 to 4% of the oral dose. In study 6-5 the peak plasma level after subcutaneous injection of 100 mg of PPS was estimated to be 2.5 to 3.8 ug/ml at 120 minutes.

TOXICOLOGY:

It is stated in this submission that the toxicology studies performed have shown that Elmiron has a low potential for causing toxic side effects. After acute and multidose administration of Elmiron at selected toxic doses above 5 mg/kg the most common signs, when present, were related to anticoagulant activity or, on parenteral injection to local irritation. In the acute toxicity studies after oral LD50 being greater than 35 g/kg in rats and mice this drug was "practically non-toxic". The multidose toxicity studies showed a low toxicity in rats and in primates (baboons and rhesus monkeys) orally or parentally administered. Mutagenicity studies did not show mutagenic activity "in either the micronucleus assay or the Ames Test". No oncogenic studies were performed, but the sponsor states that "on the basis of its chemical structure and lack of mutagenic action, pentosan polysulfate sodium is unlikely to be a carcinogen". In reproduction studies (Segment I and III types) in rats and in teratogenic studies (Segment II) in mice and rabbits "there was no evidence of adverse effect on reproduction or development of the fetus". Elmiron is not a sensitizer after sensitization studies to guinea pig.

More detailed comments about toxicology of this drug will be found in the Pharmacology review.

CONTENT OF THIS SUBMISSION:

The sponsor submits this New Drug Application with the results of studies performed under the previously submitted IND This NDA consists of 20 volumes as follows:
One volume of the summary information.
One volume chemistry, manufacturing and control section
One volume pharmacokinetic section
Five volumes of non-clinical pharmacology and toxicology sections.
Four volumes of clinical data sections (vols. 9, 10, 11, 12 of 20).
Eight volumes of technical section for statistics.

This submission is related to the final evaluation of two controlled, double-blind studies (Study Protocols E-001 and E-002).

Baker Cummins, the sponsor, includes in this application (vol. 12 of 20 vols) their comments about the numerous "Compassionate Use Program" requested by physicians for the use of this drug in patients suffering interstitial cystitis. As per figures from the sponsor more than 1274 interstitial cystitis patients were treated under this "Compassionate program".

RATIONALE:

Interstitial cystitis is a syndrome characterized by the symptoms of urinary urgency, urinary frequency, nocturia, lower abdominal and perineal pain and/or discomfort. It occurs in the absence of infection or other known pathologic process such as carcinoma in situ, radiation or chemical cystitis. The etiology of this disease has not been proved yet although several theories has been postulated; the following statements reproduced from the sponsor of this NDA 20-193 describes the rationale for the use of Elmiron in the treatment of Interstitial Cystitis according to the investigators of this study.

"Although its etiology has not been definitely established, it has been postulated that interstitial cystitis is caused by a dysfunctional epithelium which becomes permeable and allows the leak of urinary solutes across the transitional cells. In both animals and humans, it has been shown that the principal barrier to permeability is the surface glycosaminoglycans. A permeable bladder epithelium can result in diffusion of irritating components from normal urine through the bladder wall to set up a chronic inflammatory condition initiating the symptoms of pain, urgency, and frequency."

"Its mechanism of action is through its ability to adhere to the bladder surface and substitute for the natural glycosaminoglycans in patients with interstitial cystitis. By repair of the permeable bladder epithelium, diffusion of the irritating components from normal urine through to the bladder wall is decreased and the symptoms of interstitial cystitis are ameliorated."

BACKGROUND INFORMATION:

Elmiron has not been available for unrestricted sale and use in the United States. It has been marketed and used in Europe and other parts of the world for the treatment and prophylaxis of thrombosis and hyperlipidemia.

The sponsor states that from 1985 through 1989 there were sales of ampules of 100 mg each; tablets of 25 mg each, and capsules of 100 mg each in the following countries:

<u>COUNTRY</u>	<u>APPROVAL DATE</u>	
	<u>Ampules</u>	<u>Capsules/Tablets</u>
Argentina	1965	1965
Austria	1962	1963
Bulgaria		1973
E. Germany		1984
Finland		1989
France	1961	1961
W. Germany	1961	1961
Hong Kong	1968	1968
Hungary	1980	1979
Italy	1962	1964
Portugal	1962	1964
South Africa	1967	1967
Spain	1961	1962

The sponsor states that this data was obtained from the manufacturer and supplier of Elmiron.

It is stated also that the regulatory body in W. Germany reported the occurrence of reversible thrombocytopenia in patients treated with high doses of Elmiron by injection, but has not been observed when Elmiron was administered exclusively by the oral route. It is suggested that this reaction could be due to platelet aggregating antibodies most of which cross-react with heparin. Other side-effects reported between 1963 and 1990 to the

were:

- 4 Loss of hair
- 1 Subcutaneous fatty atrophy
- 1 Leucocytopenia and retarded nail growth
- 1 Nausea and vomiting
- 1 Drug rash
- 30 Heparin-induced thrombocytopenia (of these, one occurred in Germany and the remaining in France).

CLINICAL TRIALS:

TITLE OF PROTOCOL:

"THE EVALUATION OF ELMIRON (PENTOSAN POLYSULFATE SODIUM) IN
THE TREATMENT OF THE SYMPTOMS OF INTERSTITIAL CYSTITIS".
Protocol E-001

STUDY DESIGN:

The protocol for this study was designed as a multicentric, double-blind, placebo controlled, parallel group evaluation for the symptomatic treatment of patients with interstitial cystitis. Patients were randomized to be treated with Elmiron or placebo in accordance with a computer generated random code.

BACKGROUND INFORMATION:

Elmiron (pentosan polysulfate sodium) was granted an orphan drug designation for the treatment of interstitial cystitis on August 7, 1985 in accordance with the Federal Food, Drug and Cosmetic Act, Section 526.

On 1/29/1987, this M.O. reviewed this protocol submitted under IND which incorporated some revisions from the original one, as suggested by this Division. The protocol was considered appropriate for the objective enunciated in the title of it except for some minor modifications we suggested to the sponsor. They accepted our suggestions and requests which were incorporated to the protocol under the correspondent amendments.

OBJECTIVE:

To evaluate the safety and efficacy of Elmiron, 100 mg t.i.d. compared to placebo t.i.d. in the relief of symptoms caused by documented interstitial cystitis in a 3-month, randomized, double blind trial with at least 120 patients with the moderate syndrome of interstitial cystitis and as many severe patients as became available.

METHODS OF INVESTIGATION:

This multicentric study was performed in 5 centers, with each of the 5 centers enrolling 24 moderate syndrome patients. Patients were treated by a double-blind method during 3 months, at the end of that period the blind phase of the study terminated.

The design of this study was considered appropriate.

MATERIALS:

Investigative drug: Elmiron tablets, 100 mg administered 1 tablet
t.i.d.

Placebo: Tablets similar to the Elmiron administered as 1 tablet
t.i.d.

SELECTION OF PATIENTS:

Number: The protocol was designed to include at least 120 patients of those described as "with moderate disease". Patients with "severe degree of disease" to be accepted into the study as they became available for a separate evaluation.

Age: Patients between the ages of 18 and 75. Sex: Males and females.

The definition of patients for each of the two groups was:

a) Moderate disease:

Patients with bladder capacity under anesthesia over 400 ml.
Voiding profiles showing 18 or fewer voids per day.
Average voided volume of at least 75 ml.

b) Severe disease:

Bladder capacity under anesthesia less than 400 ml.
Voids per day greater than 18.
Average voided volume less than 75 ml.

INCLUSION CRITERIA:

To be included in the study, patients had to satisfy the following inclusion criteria with symptoms being present for at least one year:

- 1) Urgency- at least moderate on the analog scale attached to the protocol.
- 2) Frequency- at least 10 voids/24 hours.
- 3) Nocturia- Void at least 2 times per night.
- 4) Pain- patients to have pain recorded on the analog scale.
- 5) Previous therapy
therapy (chloropactin, hydrodilation, or DMSO)
- 6) Have an average voided volume per void of 200 ml or less measured over a 3 day period.
- 7) Have a negative urine culture and cytology.
- 8) Have a cystoscopic examination under anesthesia (80 cm of water and 1 minute distension) showing petechial hemorrhages or ulcers with gross blood in the fluid return and a bladder capacity of 800 ml or less.

EXCLUSION CRITERIA:

1. Less than 18 years of age.
2. Pregnancy
3. Patients pre-menopausal and not practicing effective means of birth control.
4. Evidence of active peptic ulcer disease.
5. Bleeding diathesis.
6. Patients receiving anticoagulant therapy.
7. Patients with chronic use of narcotics.
8. Patients known allergic to sodium pentosanpolysulfate.
9. Patients unable to complete the study, or not available for follow-up examinations or unable to follow instructions

- 10. Patients using artificial sweeteners.
- 11. Lactating mothers.
- 12. Patients with any signs of the following:
 - recurrent bacteriuria.
 - obvious neurological impairment.
 - history of pelvic irradiation or previous treatment with known bladder irritants.
 - bladder carcinoma.
 - urinary TB.
 - schistosomiasis.
- 13. Patients treated with Elmiron within the past 6 weeks.

CLINICAL INVESTIGATORS:

	Patients Enrol.	Comp.
Phillip Hanno, M.D. Hospital of the University of PA. Philadelphia, PA 19104.	31	24
S. Grant Mulholland, M.D. Thomas Jefferson University Hospital Philadelphia, PA 19107.	12	12
C. Lowell Parsons, M.D. University of California Medical Ctr. San Diego, CA 92103	27	25
Grannum R. Sant, M.D. Tufts University School of Medicine Boston, MA 02111	24	23
David R. Staskin, M.D. Boston University School of Medicine Boston, MA 02111	16	14
<u>Total patients</u>	110	98

These investigators were qualified to be in these studies as per their CV.

The sites of the investigations for this study E-001 were:

Investigator	Site
Phillip Hanno, M.D.	1
S. Grant Mulholland, M.D.	2
C. Lowell Parsons, M.D.	3
Grannum R. Sant, M.D.	4
David R. Staskin, M.D.	5

STUDY MONITOR:

James T. Baldini, pH.D.

STATISTICIAN:

J. Richard Trout, pH.D.

STUDY EVALUATION:

Forms to be completed by the patient or the investigator:

Flow sheet.
Patient History Form.
Initial questionnaire.
Pretreatment Report (1)
Pretreatment Report(2).- Cystoscopic Evaluation
Volume voiding Profile
Pain and Urgency Scales
Laboratory Reports
Drug Use Record Form.
Follow-up Questionnaire (Patient's assessment of overall improvement)
Report of Adverse Reactions
Investigator's Evaluation of Overall Improvement

NOTE: REPRODUCTIONS OF THESE FORMS ARE ATTACHED TO THIS REVIEW IN THE FOLLOWING PAGES:

MEDICAL MARKET SPECIALTIES, INC.
EVALUATION OF ELMIRON FOR TREATMENT OF INTERSTITIAL CYSTITIS
FLOW SHEET

PATIENT NAME _____

DATE _____

PATIENT NO. _____
(if enrolled)

PRETREATMENT:

1. Provide prospective patient with volume voiding profile form to complete 3-day record before coming for evaluation.
2. At first office visit, explain study to patient and complete informed consent form if patient desires to enter study.
3. Have patient complete initial questionnaire.
4. Have patient complete pain and urgency analog scales.
5. Take patient history and complete physical exam.
6. Take specimens for laboratory work.
7. Do cystoscopic examination and complete report form.
8. Complete pretreatment report form.
9. On basis of pretreatment report data, is patient eligible for entry into study?
 Yes [] No [] *(If no, consider compassionate use program)*
10. If patient is eligible, is disease Moderate [] or Severe [].
11. If Moderate, assign patient next treatment number in 1 to 24 series.
12. If Severe, assign patient next treatment number in 25 to 48 series.
13. Begin drug use record form and give patient:
 - a) 3 month treatment supply
 - b) patient instruction sheet
 - c) 2 pain/urgency analog scale forms
 - d) 2 volume voiding profile forms
 - e) appointment card for visit at three months

VISIT AT THREE MONTHS

1. Do physical examination, discuss disease status, and review volume voiding profiles with patient.
2. Have patient complete pain and urgency scales.
3. Have patient complete follow-up questionnaire.
4. Take specimens for laboratory work.
5. Collect unused drug and complete drug record form.
6. Complete investigator's evaluation of overall improvement form.
7. Review and complete case report form and mail three copies to Medical Market Specialties, Inc. The remaining copy is for your records.
8. Stop treatment for all Elmiron patients who have experienced a fair or better response and measure time to relapse before starting Elmiron treatment again on an open basis.
9. Discuss with those patients who experienced little or no response whether or not they want to continue Elmiron treatment for up to 3 more months.
10. Discuss with all placebo patients whether or not they want to begin trial with Elmiron on an open basis and if yes, begin study setting baseline parameters as in the beginning of the double-blind phase of the study with new case report form.

**ELMIRON IN INTERSTITIAL CYSTITIS
PATIENT HISTORY FORM**

INVESTIGATOR: _____

D/TE _____

PATIENT NAME: _____

PATIENT NO. _____
(if enrolled)

General Medical Status: (please print)

DISORDERS OTHER THAN INTERSTITIAL CYSTITIS.

- 1. Allergy: _____
- 2. Blood and lymphatic: _____
- 3. Cardiovascular: _____
- 4. Dermatological: _____
- 5. Endocrine: _____
- 6. Gastrointestinal: _____
- 7. Liver and biliary: _____
- 8. Musculoskeletal: _____
- 9. Nervous and neuropsychiatric: _____
- 10. Respiratory: _____
- 11. Sensory: _____

Current Medications: (please print)

Previous Medications for Interstitial Cystitis: (please print)

DRUG	DOSE	DATES	EFFICACY*

* A = Excellent, B = Good, C = Fair, D = Poor

Previous Surgery: (please print)

ELMIRON STUDY INITIAL QUESTIONNAIRE

INVESTIGATOR _____
 PATIENT NAME: _____

DATE _____
 PATIENT NO. _____
(if enrolled)

1. Do you have pain when voiding?
2. Is your pain constant?
3. Do you have pain in your lower abdomen?
4. Do you have pain in the vaginal/urethral area?
5. How long have you had these pains? _____ yr _____ mo
6. Do you get up at night to urinate?
 a) How often? _____
 b) How long have you done this? _____ yr _____ mo
 c) Do you get a good night's sleep?
7. How often do you urinate during the day?
8. Does walking aggravate your symptoms?
9. Does sexual intercourse aggravate your symptoms?
10. Do you take artificial sweeteners in:
 coffee, tea, cereal, etc.
 Tab, Diet Pepsi, etc.

	YES	NO
1.	[]	[]
2.	[]	[]
3.	[]	[]
4.	[]	[]
5.	[]	[]
6.	[]	[]
7.	[]	[]
8.	[]	[]
9.	[]	[]
10.	[]	[]

MEDICAL MARKET SPECIALTIES, INC.
CASE REPORT FORM PROTOCOL E-001
PLACEBO-CONTROLLED STUDY OF ELMIRON FOR INTERSTITIAL CYSTITIS

INVESTIGATOR: _____

DATE _____

PATIENT NAME (or I.D.) _____

PATIENT NO. _____
(if enrolled)

PRETREATMENT REPORT (pg. 1 of 2)

AGE: _____ (must be 18 yrs. or more)

SEX: M () F ()

RACE: Caucasian () Black () Other () _____ (specify)

Duration of Interstitial Cystitis: _____ yrs. _____ mos. (must be 1 yr. or more)

SYMPTOM REQUIREMENTS:

YES	NO
[]	[]
[]	[]
[]	[]
[]	[]

1. Frequency at least 10 voids per day?
2. Urgency at least moderate on urgency scale?
3. Nocturia at least 2 voids per night?
4. Average voided volume less than 200 ml (3 days)?

EXAMINATION REQUIREMENTS:

[]	[]
[]	[]
[]	[]

5. Urinalysis normal?
6. Urine cytology negative?
7. Urine culture negative?

IF ANY ONE OF QUESTIONS 1 TO 7 IS ANSWERED "NO", PATIENT IS NOT ELIGIBLE FOR STUDY.

EXCLUSIONS:

[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
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[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]
[]	[]	[]	[]

8. Less than 18 yrs. of age?
9. Pregnant?
10. Premenopausal, not practicing effective birth control?
11. Evidence of active peptic ulcer disease?
12. Bleeding diathesis?
13. Recurrent bacteriuria?
14. Obvious neurological impairment?
15. Previous treatment with bladder irradiation or implants?
16. Bladder carcinoma?
17. Schistosomiasis or urinary TB?
18. Lactating mother?
19. Known allergy to Elmiron (sodium pentosanpolysulfate)?
20. Receiving anticoagulant therapy?
21. Making chronic use of narcotics?
22. Using artificial sweeteners?
23. Will not be available to complete study?
24. Unable to follow instructions?
25. Treated with Elmiron within past 6 weeks?
26. Response to previous conventional therapy successful?
 (hydrodistension, chloropectin, or DMSO)

IF ANY ONE OF ITEMS 8 TO 24 IS ANSWERED "YES", PATIENT IS NOT ELIGIBLE FOR STUDY.

**ELMIRON IN INTERSTITIAL CYSTITIS
PRETREATMENT REPORT (pg. 2)**

INVESTIGATOR: _____

DATE _____

PATIENT NAME: _____

PATIENT NO. _____
(if enrolled)

CYSTOSCOPIC EVALUATION

(Conditions: 1 minute distension; 90 cm. of water; under anesthesia)

OBSERVATION	SEVERITY*			
Bladder Capacity _____ cc				
Bloody Drainage of Fluid	3	2	1	0
Fissures, Linear Scars or Granulations	3	2	1	0
Petechial Hemorrhages	3	2	1	0
Hunner's Ulcer Yes [] No [] Number _____ Size _____ mm				
Other Abnormalities Yes [] No [] If Yes, describe _____				

*SEVERITY SCORE (circle appropriate number):

- 3 many/extensive/gross
- 2 moderate
- 1 few/limited/scant
- 0 none

DOES PATIENT HAVE

- 1. Bladder capacity less than 800cc?
- 2. Gross blood in fluid return?
- 3. Petechial hemorrhages?

YES	NO
[]	[]
[]	[]
[]	[]

A "NO" ANSWER TO ANY ONE OF QUESTIONS 1 TO 3 MAKES THE PATIENT INELIGIBLE FOR THE STUDY.
(consider compassionate use program for patient)

PATIENT GROUP SEPARATION:

PATIENT GROUP SEPARATION:	MODERATE PATIENTS (patient # 1-24)	SEVERE PATIENTS ** (patient # 25-48)
ANESTHETIC BLADDER CAPACITY	at least 400 ml	less than 400 ml
AVERAGE VOIDED VOLUME	at least 75 ml	less than 75 ml
VOIDS PER DAY	18 or fewer	more than 18

**ANY ONE OF THESE CRITERIA AUTOMATICALLY PLACES THE PATIENT IN THE SEVERE GROUP.

**ELMIRON IN INTERSTITIAL CYSTITIS
PAIN & URGENCY SCALES**

INVESTIGATOR: _____

DATE _____

PATIENT NAME: _____

PATIENT NO. _____

TREATMENT MONTH: 0 1 2 3 6 9 12 15 18 21 24

SCALE ONE **PAIN**

NONE MILD MODERATE SEVERE

0 1 2 3 4 5

SCALE TWO **URGENCY (URINARY PRESSURE TO URINATE)**

NONE MILD MODERATE SEVERE

0 1 2 3 4 5

Dear Patient:

Please rate by circling the number that best describes

on Scale One above, the bladder pain, if any, you have generally had during the past month

AND

on Scale Two above, the urinary pressure or urgency, if any, you have generally had during the past month.

**ELMIRON IN INTERSTITIAL CYSTITIS
LABORATORY REPORTS**

INVESTIGATOR: _____

DATE _____

PATIENT NAME: _____

PATIENT NO. _____

TREATMENT MONTH: 0 3 6 - 9 12 15 18 21 24

HEMATOLOGY & BLOOD CHEMISTRY:

URINE:

HCT (%)

Color

RBC (million/mm³)

pH

Hb (gm/100ml)

Spec. Gravity

WBC (100/mm³)

Protein (+/-)

Neut. %

Glucose (+/-)

Lymph. %

Acetone (-/-)

Mono. %

Creatinine (mg %)

Eosin. %

Culture (+/-)

Platelets (100/mm³)

PT (sec.)

LDH (units/ml)

Alk. Phos. (units)

SGOT (mu/ml)

SGPT (mu/ml)

BUN (mg %)

Bilir. (mg %)

Glucose (mg %)

Ca (mg %)

K (mg %)

**RANDOMIZED PROSPECTIVE STUDY OF EFFICACY OF SODIUM PENTOSANPOLYSULFATE
IN THE TREATMENT OF INTERSTITIAL CYSTITIS**

FOLLOW-UP QUESTIONNAIRE

NAME: _____

DATE _____

PATIENT NO. _____

(Please circle the word that best answers the question)

1. Do you notice any difference in pressure to urinate? Yes No

2. If you answered "yes" to Question #1, is the pressure to urinate Better Worse

3. If you answered "better", which best describes the improvement?
 - a) slight improvement (25%)
 - b) moderate improvement (50%)
 - c) great improvement (75%)
 - d) symptoms are gone (100%)

4. How often do you urinate? _____

5. Do you still have pain with urination? Yes No

6. If the pain is better, is it
 - a) slight improvement (25%)
 - b) moderate improvement (50%)
 - c) great improvement (75%)
 - d) pain gone (100%)

7. Do you get up at night to void? Yes No
If "yes", how often? _____

8. Do you think you get a better night's sleep now than before the treatment? Yes No

9. Do you feel that you are improved overall since the treatment started? Yes No

10. If you feel improved, which answer best describes the improvement over the past month?
 - a) slight improvement (25%)
 - b) moderate improvement (50%)
 - c) great improvement (75%)
 - d) complete cure (100%)

**ELMIRON IN INTERSTITIAL CYSTITIS
REPORT OF ADVERSE REACTION**

INVESTIGATOR: _____

DATE _____

PATIENT NAME: _____

PATIENT NO. _____

(PLEASE PRINT)

TYPE REACTION: _____

TREATMENT: _____

OUTCOME: *(Indicate Severity)* _____

RELATION TO STUDY TREATMENT:

POSSIBLE [] PROBABLE [] NOT LIKELY [] OTHER CAUSE []

COMMENTS: _____

ELMIRON IN INTERSTITIAL CYSTITIS
INVESTIGATOR'S EVALUATION OF OVERALL IMPROVEMENT

INVESTIGATOR: _____

DATE _____

PATIENT NAME: _____

PATIENT NO. _____

(Circle number that best describes your opinion of patient's overall improvement at end of 3-month study)

- 1. WORSE: patient's symptoms generally more severe than at start of study
- 2. NO CHANGE: patient's symptoms essentially unchanged since start of study
- 3. FAIR: about a 20% improvement in one or more symptom(s)
- 4. GOOD: about 30 to 40% improvement in two or more symptoms
- 5. VERY GOOD: about 70% improvement in two or more symptoms
- 6. EXCELLENT: about 90% or more improvement in essentially all symptoms

INVESTIGATOR _____

Initial questionnaire:

This questionnaire was completed by the patient at the initial evaluation to give to the investigator all the information related to the inclusion requirements. Answers to questions were compared to similar answers to questions contained in the follow-up questionnaire.

Pretreatment report: Pretreatment report (page 1 of 2)Cystoscopic evaluation. (page 2 of 2)

(1) This form was to be completed prior the initiation of treatment and is one of the fundamental examination requirements as inclusion criteria for a positive diagnosis of interstitial cystitis.

(2) Cystoscopic evaluation: This form provided information during the cystoscopic examination of the bladder capacity, the presence in the bladder mucosa of fissures, linear scars, glomerulations, petechial hemorrhages, Hunner's Ulcer, etc.. and principally a sign that must be present, the gross blood in the fluid return

Volume Voiding Profile:

This form was completed by the patient before treatment, and at the end of the 1st, 2nd, and 3rd months of treatment. This form provided information concerning changes in average voided volume, frequency and nocturia observed before treatment and at the end of the 1st, 2nd and 3rd months of treatment with a record of the time and quantity of all urination during waking hours and the number of voidings during sleeping hours over 3 consecutive days.

Pain and Urgency Scales

Pain and urgency were included in one sheet showing the correspondent scales. This form was completed in the same manner as the volume voiding profile, that is, before starting the treatment, and at the end of 1, 2 and 3 months. The scales for pain and urgency allowed the patient to report the degree of pain and urgency on a scale from 0 to 5, on which 0 was equivalent to none and 5 to severe.

Laboratory Reports

Routine laboratory examinations were performed before the initiation of treatment and at the end of the three month treatment period.

Tests included urinalysis, CBC, blood chemistries, liver function tests and prothrombin time.

Laboratory tests performed again at the end of 12 months.

Follow-up Questionnaire:

This questionnaire was completed by the patient at the end of the double-blind treatment period.

Patients were asked if they felt improved overall since the start of the treatment, and if so to define the improvement as:

Slight.....25%
Moderate.....50%
Great.....75%
Complete cure..100%

Through this questionnaire patients evaluated the changes, if any, in relation to urgency and pain, number of voidings during the day, number of voidings at night, and if they got a better night's sleep after treatment than they did before treatment. These answers were to be compared to the answers of same questions contained in the initial questionnaire.

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3 OF 7

Report of Adverse Reaction:

This case report form included the report of any adverse reactions including the type of reaction, treatment, outcome, etc. and relation to treatment as possible, probable, not likely, etc. It is specified that patients were not questioned by the investigator concerning side effects. Reports of side effects were volunteered by the patient.

Investigator's Evaluation of Overall Improvement:

This form was completed by the investigator after examining the patient and reviewing the data provided in voiding profiles and pain and urgency scales while patient was maintained in the double-blind period. The investigator used the following scale:

- a) WORSE - Patient's symptoms were generally more severe than at the start of the study.
- b) NO CHANGE - Patient's symptoms essentially unchanged since the start of the study.
- c) FAIR - About a 20% improvement in one or more symptoms.
- d) GOOD - About 30% to 40% improvement in two or more symptoms.
- e) VERY GOOD - About 70% improvement in two or more symptoms.
- f) EXCELLENT - About 90% or more improvement in essentially all symptoms.

EXAMINATION REQUIREMENTS:

- a) All patients completed the micturitional profile with documented 10 voids per day and an average voided bladder volume of less than 200 ml (3 days).
- b) Urinalysis and negative urine culture and cytology.
- c) Cystoscopic examination under anesthesia by the investigator (80 cm of water and 1 minute distension) showing petechial hemorrhages or ulcers with gross blood in the fluid return and a bladder capacity of less than 800 ml. No patient was randomized for entry until at least 6 weeks after cystoscopy. This waiting period was necessary because the dilation of the urethra by the cystoscope and/or the hydrodistension of the bladder produced by the water used for the cystoscopic examination may have induced disease remission. If the patient have been relieved of symptoms during these six weeks, he/she should be excluded from the study. If symptoms recurred, the patient could be included in the study. Once the test treatment was initiated, the patient should not have taken any medication that may modify bladder function or have been treated by any of the conventional methods of treatment for this disease e.g. local urethral and/or bladder treatments.
- d) Biopsy was not required.
- e) Cystometrograms were optional.

DOSAGE AND ADMINISTRATION:

After the pre-treatment evaluation, patients were randomly assigned to the treatment Elmiron 100 mg tablets t.i.d. or to placebo tablets 1 tab. t.i.d. This double-blind treatment lasted three months.

All patients that improved at the end of the 3-month treatment period were asked to stop treatment so that time to relapse of symptoms could be measured. Of the patients reporting no improvement during the 3-month double-blind period, those who received Elmiron were given the opportunity to continue on Elmiron for an additional 3 months if they so desired, and the placebo patients were started on Elmiron on an open label basis for a 3-month treatment period. All patients experiencing improvement were given the opportunity to continue on Elmiron for up to two years. Patient follow-up was continued every 3 months during the 2-year period.

During the double blind phase, the response variables of pain, urgency, frequency of urination, and the total urine volume was recorded on a monthly basis for the three-month period. At each month and at the final visit for each patient, the change from pre-treatment was analyzed for each of these response variables.

In relation to the dose range for this drug the sponsor states the following: "In the studies that preceded the clinical studies of the present application and which are reviewed as a part of this volume, the total daily doses used were 300 or 400 mg given in 2 or 3 divided doses. Elmiron appeared to show efficacy at these dose levels and there did not seem to be a clinical difference between 300 and 400 mg. Consequently, based on the results of these earlier studies 300 mg per day was chosen for the clinical studies which form the basic support for the present application."

CRITERIA FOR DETERMINING EFFICACY:

The variables used for the determination of Elmiron efficacy in order of importance were:

- The patient's assessment of overall improvement compared to pretreatment.
- The investigator's assessment of overall improvement.
- Changes in pain and urgency.
- Change in nocturia.
- Change in frequency.
- Change in average voided volume.

In each case, the change from the baseline values to the values at the end of the double blind period was used as the basis for determining the efficacy of Elmiron.

All patients were seen at 0 time before start of treatment for baseline symptom measurements and laboratory values and at 12 weeks after start of treatment for measurement of the same variables.

The primary measurement used to determine effectiveness of Elmiron was the patient evaluation of overall improvement as compared to pretreatment condition. The evaluation of overall improvement made by the investigator was also considered to be a primary measure of efficacy, second only to the patient self evaluation. The individual symptoms of interstitial cystitis, i.e. frequency, urgency, pain, nocturia and average voided volume although asked to be recorded by the patient and taken into consideration for statistical purposes, are the subject of the following statement from the sponsor: "...because of the variable nature of the interstitial cystitis symptom complex among patients, in both the presence and intensity of symptoms, changes in individual symptoms are not reliable indications of improvement in this disease. The individual symptoms of interstitial cystitis, frequency, urgency, pain, and nocturia, vary widely within and between patients with variable perceived importance."

In another paragraph the sponsor affirms: "For these reasons emphasis in this study was placed on overall improvement as expressed by the patient and investigator, while the changes in specific symptomatology were only considered as supportive data."

CRITERIA FOR DETERMINING SAFETY:

Safety assessment was based on the occurrence of adverse reactions and comparison of laboratory data at baseline to endpoint of the study.

CONCOMITANT THERAPY:

Patients were not allowed to take any other drugs during the study except those that might be prescribed by the investigator for specific purposes. In the case of over-the-counter medications, only those drugs that had been approved with the investigator could be used.

All drugs taken during the study were recorded in the correspondent form.

REMOVAL OF PATIENTS FROM THE STUDY OR ANALYSIS:

Any patient who did not complete 12 weeks of treatment or who was treated by any other of the conventional treatments for interstitial cystitis (Hydrodilatation of the bladder or with DMSO) during the period of study was excluded from the evaluation of efficacy.

RESULTS OF THIS STUDY:

The following are excerpts from tables 1 to 49, pages 5-758 through 5-823G from Vol. 10 of 20 vols. as submitted from the sponsor.

Study population:

As described previously in this review, this study was designed to be multicentric with an investigator at each of the 5 centers enrolling in each center 24 patients with a moderate degree of interstitial cystitis for a grand total of 120 patients. An interim analysis of the data was obtained after about 50 patients that had completed the 3 month double-blind period. This analysis indicated to the sponsor that about 100 patients would be sufficient for determining the safety and efficacy of Elmiron compared to placebo. The enrollment was stopped with 110 patients admitted into the study

Age:

Patients in the Elmiron treatment group: 20 to 72 yrs, mean 43.3 years.
Patients in the placebo treatment group: 25 to 82 yrs, mean 45.3 years.

Number:Sex:

	54 patients in the Elmiron group-	49 female (91%);	5 male (9%)
	56 patients in the placebo group-	49 female (87%);	7 male (13%)
Total	110 patients		

Severity:

Elmiron group:	Number of patients with moderate disease	23 (41%)
	Number of patients with severe disease	31 (57%)

Placebo group:	Number of patients with moderate disease	23 (41%)
	Number of patients with severe disease	33 (59%)

Final number of patients

Patients on Elmiron that completed the study.....	51 (94%)
Patients on Elmiron that did not complete the study.(*).	3 (6%)

Patients on placebo that completed the study.....	47 (84%)
Patients on placebo that did not complete the study.....	9 (16%)

(*). These 3 patients withdrew prior to the completion of the double blind phase.

The following are the explanations given by the sponsor in relation to the reasons for not completing the study: "Of the 12 patients that withdrew early, 9 did so during the first month of treatment. Generally reasons for withdrawal were not supplied by the investigators. For three patients the reason for withdrawal was related to adverse reactions. Two of these patients were in the placebo group, one of whom experienced diarrhea, while the other experienced joint pain. The Elmiron patient who withdrew due to an adverse reaction experienced headache, nausea, severe mood swings, and suicidal ideation. One patient in the placebo group withdrew due to lack of effect." (underlined by this M.O. reviewer)

PAIN SUMMARY:

The sponsor enclosed a summary of the pain data recorded on a monthly basis tables 4 through 6, (mean figures combining the 5 sites of study).

Table 4 shows a summary of the rating of pain (0=none to 5=severe) at each month of the double blind treatment (months 0 through 3) and at the end point (end of third month).

Table 5 summarizes the change of pain from baseline (month 0) to each month of the double blind treatment and at end point.

Table 6 is a summary of patient improvement in pain.

Table 4 summarizes the rate of pain at month 0 and at the end of the third month of treatment (0=none--5=severe) as follows in combined mean figures.:

GROUP	RATING OF PAIN AT MONTH 0	RATING OF PAIN AT ENDPOINT
Elmiron	(53 patients)...3.2	(51 patients)...2.7
Placebo	(56 patients)...3.0	(50 patients)...2.8

In table 5, the change of pain from end of month 1 to end of double blind treatment (end point) was as follows (mean figures)

GROUP	END OF MONTH 1	END OF MONTH THREE
Elmiron (50 patients).....	-0.4	change from baseline -0.5
Placebo (50 patients).....	-0.1..	change from baseline -0.2

In table 6, improvement in pain in patients treated with Elmiron compared to patients treated with placebo, the changes from baseline to the end of the double blind treatment (end point) were as follows:

Elmiron group <u>improved</u> (*).....	22 patients (43%)
Elmiron group <u>not improved</u>	29 patients (57%)
Placebo group <u>improved</u> (*).....	13 patients (26%)
Placebo group <u>not improved</u>	37 patients (74%)

(*) Pain reduction of 1 point or more on pain scale.

Tables 4, 5 and 6, no statistically significant differences were found.

URGENCY SUMMARY:

The sponsor enclosed a summary of the urgency data recorded on a monthly basis in tables 7 through 9 combining the 5 sites of study

Table 7 shows a summary of rating of urgency (0=none to 5=severe) at each month of the double blind treatment period (months 0 to 3) and at the end point (end of third month).(mean combined figures from the 5 sites)

Table 8 summarizes the change of urgency from baseline (month 0) to each month and at the end point (mean combined figures from the 5 sites)

Table 9 is a summary of patient improvement in urgency in combined and percent figures..

In table 7 are summarized the changes of urgency related to the severity of this symptom, mean reduction from month 0 to end of third month in which 0=none and 5=severe as follows (mean combined figures):

GROUP	SCALE URGENCY MONTH 0	END OF THIRD MONTH
Elmiron (53 patients), rating	3.9	3.3 (51 pts)
Placebo (56 patients), rating	3.9	3.2 (50 pts)

No statistically significant treatment group differences were found.

In table 8, the change of urgency (point reduction) from baseline to the end of double-blind treatment (end point) was as follows (mean figures combined)

GROUP	END OF MONTH 1	END OF THIRD MONTH
Elmiron (50 patients)	-0.3	-0.6 (51 pts)
Placebo (50 patients)	-0.1	-0.5 (50 pts)

No statistically significant treatment group differences were found.

In table 9, is summarized the improvement in urgency in patients treated with Elmiron compared to patients treated with placebo. The changes from baseline to the end of the double-blind treatment (end of third month) were as follows (mean figures combined):

Elmiron group improved.....	20 patients (39%)
Elmiron group not improved.....	31 patients (61%)
Placebo group improved.....	23 patients (46%)
Placebo group not improved.....	27 patients (54%)

No statistically significant treatment group differences were found.

VOIDING PROFILE:

The voiding profile data were collected for each patient for a 3 day period of the time associated with each of the monthly visits (0, 1, 2, 3). These data are summarized in tables 10 through 19. (mean figures combining the 5 sites of investigation). For each of these analyses no statistically significant treatment group differences were found.

Table 10 shows a summary of the number of voids per day (24 hours) from baseline (month 0) to each of the three months of treatment and at end point

Table 11 summarizes the change of the number of voids per day (24 hrs) from baseline (month 0) to each of the three months of treatment and at end point.

Table 12 summarizes the improvement in voids per day (24 hours) from month 1 to each of the three months of treatment and at end point; by this table a patient is better if there is at least a reduction of 3 voids per day.

Table 13 summarizes the number of voids per night (defined as 12 PM to 7 AM) at each month (0 through 3) and at end point.

Table 14 summarizes the change of the number of voids per night from baseline (month 0) through each month and at the end of the third month of treatment (end point).

Table 15 displays a summary of the volume per void in c.c. at each month (0 through to 3) and at endpoint

Table 16 summarizes the change of the volume per void (c.c.) from baseline (month 0) to each of the three months of the blind treatment and endpoint.

Table 17 displays a summary of improvement in volume per void at each month and at the endpoint. By this table a patient is better if there is at least a 20 c.c. increase in volume per void.

Table 18 displays a summary of total daytime volume voided (c.c.) from month 0 through the end of the third month of treatment (endpoint).

Table 19 summarizes the change of the total daytime volume voided (cc) from baseline to the end of the third month of treatment (endpoint).

In table 10 are summarized the number of voids per day (24 hrs) at baseline and at the end of the third month of treatment (mean figures, combining the 5 sites):

GROUP	AT BASELINE	AT THE END OF THE THIRD MONTH
Elmiron (52 patients)	19.2	18.2 (51 pts)
Placebo (50 patients)	16.7	15.8 (50 pts)

In table 11, the change of the number of voids/24 hrs from baseline to the end point (mean figures, combining the 5 sites) was as follows:

GROUP	AT MONTH ONE	AT THE END OF THE THIRD MONTH
Elmiron (50 patients)	-0.9	-1.0 (50 pts)
Placebo (50 patients)	-0.7	-1.0 (50 pts)

In table 12, the improvement in voids per day (24 hrs) in combined figures was

GROUP	AT MONTH ONE	AT THE END OF THE THIRD MONTH
Elmiron <u>improved</u>	13 pts (26%)	16 patients (32%)
Elmiron <u>not improved</u>	37 pts (74%)	34 patients (68%)
Placebo <u>improved</u>	16 pts (32%)	17 patients (34%)
Placebo <u>not improved</u>	34 pts (68%)	33 patients (66%)

In table 13 the number of voids per night at baseline and at the end of the third month (endpoint) in mean combined figures was as follows:

GROUP	VOIDINGS/NIGHT AT BASELINE	VOIDINGS/ENDPOINT
Elmiron (52 patients)	from 4.3/night	to 3.6/night.(51 pts)
Placebo (55 patients)	from 3.3/night	to 2.9/night.(50 pts)

In table 14 the change of the number of voids per night from baseline to the endpoint in mean combined figures was:

GROUP	END OF MONTH 1	CHANGE AT ENDPOINT
Elmiron (50 patients)	-0.6	-0.8 (50 pts)
Placebo (50 patients)	-0.2	-0.5 (50 pts)

In table 15 the volume per void in c.c. at month 0 and at the endpoint of the treatment in mean combined figures was as follows:

GROUP	AT MONTH 0	AT THE END OF THIRD MONTH
Elmiron (52 patients)	89.2 cc	96.0 cc (51 pts)
Placebo (56 patients)	91.1 cc	100.6 cc (50 pts)

In table 16 the change of the volume per void (cc) from beginning of treatment at month one to the end of the third month in mean combined figures was:

GROUP	AT MONTH ONE	AT THE END OF THIRD MONTH
Elmiron (50 patients)	from 9.5 cc	to 9.8 cc (50 pts)
Placebo (50 patients)	from 5.3 c.c.	to 7.6 cc (50 pts)

In table 17 the improvement in volume per void is summarized. By this table a patient improved if there is at least a 20 cc increase in volume per void

GROUP	AT MONTH ONE	AT THE END OF THIRD MONTH
Elmiron	improved 13 pts.(26%)	improved 15 pts (30%)
Elmiron	<u>not improved</u> 37 pts.(74%)	<u>not improved</u> 35 pts (70%)
Placebo	improved 10 pts.(20%)	improved 10 pts (20%)
Placebo	<u>not improved</u> 40 pts.(50%)	<u>not improved</u> 40 pts (80%)

In table 18 the summary of total daytime volume voided (cc) from month 0 through the end of the third month of treatment was (mean figures, combining the 5 sites of investigation):

GROUP	BASELINE	END OF THIRD MONTH
Elmiron (52 patients)	1235.2 cc	1268.6 cc (51 pts)
Placebo (56 patients)	1094.2 cc	1095.8 cc (50 pts)

In table 19 the summary on change of the total daytime volume voided (cc) from beginning of treatment to the end of the third month was somewhat confusing, the following is a reproduction of the statement from the sponsor: "An examination of the means for each site (Table 19) shows that the result from site 2 was very different from that of the other sites. For example, at end point for site 2 the mean change for the placebo treatment group was 439.6 cc compared to -213.1 cc for the Elmiron group. For the remaining sites the treatment group means were either similar or showed the Elmiron group to have an increase greater than that of the placebo group. Overall sites the Elmiron group had a mean increase in daytime volume of 60.1 cc while the placebo group had a mean decrease of 20.1 cc." (sic).

The following is the reproduction of the figures provided by the sponsor in this table 19 under the title:

"Summary of total daytime volume voided (cc). Change from baseline"
(mean combined)

GROUP	END OF FIRST MONTH	END OF THIRD MONTH
Elmiron (50 patients)	114.6 cc	60.1 (50 pts)
Placebo (50 patients)	-14.5 cc	-6.5 (45 pts)

OVERALL EVALUATIONS

OVERALL EVALUATIONS OF EFFICACY:

Tables 20 through 23 summarize the 6 overall evaluations for efficacy:
 Table 20 summarize the patient response in relation to pain and urgency in rating scale and final evaluation. This table displays also the Overall patient evaluation regarding pain, urgency and pressure and the Overall investigator evaluation for these symptoms. These responses are classified as Better or Not Better after treatment with Elmiron or Placebo in relation to the combined number of patients in the five sites of investigation and the combined percentage of patients per each of the responses.

Table 21-A displays the Overall evaluation summary by baseline severity of disease (patients classified as with Moderate severity of disease) and patient's response to Pain - Based on change in rating scale, Pain - Based on patient's final evaluation, Urgency - Based on change in rating scale, Pressure - Based on patient's final evaluation and finally the Overall Patient Evaluation and the Overall Investigator Evaluation classified as Better or Not Better in the scale as well as in percent in patients treated with Elmiron or Placebo..

Table 21-B displays the Overall evaluation summary by baseline severity of disease (patients classified as with Severe severity of disease) and patient's response to Pain Based on change in rating scale, Pain Based on patient's final evaluation, Urgency-Based on change in rating scale, Pressure-Based on patient's final evaluation, and finally the Overall Patient Evaluation and the Overall Investigator Evaluation classified as Better or Not Better in the scale as well in percent in patients treated with Elmiron or Placebo.

Table 22 summarizes the analyses of the percent improvement for pain and urgency evaluated by the patient as well as the Overall patient evaluation and the Overall investigator evaluation of these symptoms in mean and combined number of patients in the five sites of investigation.

Table 23 shows a comparison of patient's Perception of Overall improvement classified as Better or Not Better in number of patients and percent of their response to Pain - Based on change in rating scale, Pain - Based on their final evaluation, Urgency - Based on change in rating scale, Pressure - Based on patient's final evaluation and the Overall Investigator Evaluation for these symptoms.

This table summarizes also the Number of voids per day change from baseline to endpoint, Volume per void change from baseline to endpoint and finally the Total volume voided change from baseline to endpoint

NOTE:

At this time it is interesting to observe the foot note that appeared in tables 20, 21A, 21B, 22 and 23 which stated: "Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis". If pain was considered an "inclusion criteria" (see this section on page 8 of this review), it is difficult to accept why in many of the other tables the results of the treatment to this symptom are evaluated and in these five tables of the "OVERALL EVALUATIONS" some patients were excluded because they "did not have pain at baseline". Pain was an absolute criteria for study-inclusion.

The following are reproductions of these tables as submitted by the sponsor. Independently of the final comments by this M.O., it should be noted that the total number of patients tabulated in each study are not coincident in some tables with the number accepted to be included

TABLE 20
OVERALL EVALUATION SUMMARY

Treatment Group		Site					Combined	Treatment Group Comparison (p-value)
		1	2	3	4	5		
<u>Response: Pain-Based on Change In Rating Scale (1)</u>								
Elmiron	Better	6	2	6	6	3	22 (46%)	0.12
	Not Better	7	5	7	4	3	26 (54%)	
Placebo	Better	5	3	2	3	0	13 (29%)	
	Not Better	4	3	10	8	7	32 (71%)	
<u>Response: Pain-Based on Patient's Final Examination (1)</u>								
Elmiron	Better	6	0	4	3	1	14 (27%)	0.11
	Not Better	8	6	9	8	6	37 (73%)	
Placebo	Better	3	0	1	2	1	7 (14%)	
	Not Better	9	6	12	9	7	43 (86%)	
<u>Response: Urgency-Based on Change In Rating Scale</u>								
Elmiron	Better	5	0	4	8	3	20 (39%)	0.51
	Not Better	9	6	9	3	4	31 (61%)	
Placebo	Better	5	3	4	5	6	23 (46%)	
	Not Better	7	3	9	7	1	27 (54%)	
<u>Response: Pressure Based on Patient's Final Evaluation</u>								
Elmiron	Better	7	0	3	1	1	12 (22%)	0.09
	Not Better	8	6	10	11	7	42 (78%)	
Placebo	Better	3	0	1	1	1	6 (11%)	
	Not Better	13	6	13	11	7	50 (89%)	
<u>Response: Overall Patient Evaluation</u>								
Elmiron	Better	8	0	4	1	2	15 (28%)	0.04
	Not Better	7	6	9	11	6	39 (72%)	
Placebo	Better	2	1	1	2	1	7 (13%)	
	Not Better	14	5	13	10	7	49 (87%)	

(1) Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis.

TABLE 20 (CONT'D)

Response: Overall Investigator Evaluation

<u>Treatment Group</u>		<u>Site</u>					<u>Combined</u>	<u>Treatment Group Comparison (p-value)</u>
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>		
Elmiron	Better	6	0	4	2	2	14 (26%)	0.04
	Not Better	9	6	9	10	6	40 (74%)	
Placebo	Better	2	1	1	1	1	6 (11%)	
	Not Better	14	5	13	11	7	50 (89%)	

TABLE 21A

OVERALL EVALUATION SUMMARY
 BY BASELINE SEVERITY OF DISEASE
 SEVERITY OF DISEASE = MODERATE

<u>Response</u>	<u>Outcome</u>	<u>Elmiron</u>	<u>Placebo</u>	<u>Treatment (2) Group Comparison (p-value)</u>
Pain-Based on Change (1) In Rating Scale	Better	7 (47%)	5 (25%)	0.19
	Not Better	10 (53%)	15 (75%)	
Pain-Based on (1) Patient's Final Evaluation	Better	5 (24%)	3 (15%)	0.70
	Not Better	16 (76%)	18 (85%)	
Urgency-Based on Change In Rating Scale	Better	9 (43%)	10 (45%)	1.00
	Not Better	12 (57%)	12 (55%)	
Pressure-Based on Patient's Final Evaluation	Better	3 (13%)	3 (13%)	1.00
	Not Better	20 (87%)	20 (87%)	
Overall Patient Evaluation	Better	6 (26%)	4 (17%)	0.72
	Not Better	17 (74%)	19 (83%)	
Overall Investigator Evaluation	Better	6 (26%)	4 (17%)	0.72
	Not Better	17 (74%)	19 (83%)	

- (1) Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis.
 (2) Fisher's Exact test.

TABLE 218

OVERALL EVALUATION SUMMARY
 BY BASELINE SEVERITY OF DISEASE
 SEVERITY OF DISEASE = SEVERE

<u>Response</u>	<u>Outcome</u>	<u>Elmiron</u>	<u>Placebo</u>	<u>Treatment⁽²⁾ Group Comparison (p-value)</u>
Pain-Based on Change ⁽¹⁾ In Rating Scale	Better	13 (45%)	8 (32%)	0.42
	Not Better	16 (55%)	17 (68%)	
Pain-Based on ⁽¹⁾ Patient's Final Evaluation	Better	9 (30%)	4 (14%)	0.31
	Not Better	21 (70%)	25 (86%)	
Urgency-Based on Change In Rating Scale	Better	11 (37%)	13 (46%)	0.60
	Not Better	19 (63%)	15 (54%)	
Pressure-Based on Patient's Final Evaluation	Better	9 (29%)	3 (9%)	0.06
	Not Better	22 (71%)	30 (91%)	
Overall Patient Evaluation	Better	9 (29%)	3 (9%)	0.06
	Not Better	22 (71%)	30 (91%)	
Overall Investigator Evaluation	Better	8 (26%)	2 (6%)	0.04
	Not Better	23 (74%)	31 (94%)	

(1) Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis.

(2) Fisher's Exact test.

TABLE 22
 PRIMARY EFFICACY MEASURES
 PERCENT IMPROVEMENT

Response: Pain

Treatment Group	Statistic	Site					Combined	Treatment Group Comparison (p-value)
		1	2	3	4	5		
Elmiron	Mean	79.2	18.8	54.2	52.1	33.3	56.0	0.20
	Std Dev	10.2	.	24.6	35.7	14.4	28.1	
	n	6	1	6	6	3	22	
Placebo	Mean	45.0	25.0	41.7	37.5	33.3	36.9	
	Std Dev	20.9	0.0	28.9	30.6	14.4	21.3	
	n	5	4	3	5	3	20	

Response: Urgency

Elmiron	Mean	37.5	-8.3	18.3	11.4	9.4	17.5	0.96
	Std Dev	36.4	12.9	27.3	20.5	18.6	29.4	
	n	14	6	13	11	8	52	
Placebo	Mean	22.5	12.5	8.3	13.5	12.5	13.8	
	Std Dev	29.9	20.9	24.6	22.3	18.9	23.5	
	n	10	6	12	12	8	48	

TABLE 22 (CONT'D)

Response: Overall Patient Evaluation

Treatment Group	Statistic	Site					Combined	Treatment Group Comparison (p-value)
		1	2	3	4	5		
Elmiron	Mean	40.4	3.1	22.1	6.8	17.2	20.5	0.30
	Std Dev	34.7	7.7	28.0	16.2	20.0	27.8	
	n	13	6	13	11	8	51	
Placebo	Mean	18.8	20.8	12.5	15.6	15.6	16.1	
	Std Dev	23.0	18.8	22.6	22.1	18.6	20.8	
	n	10	6	12	12	9	48	

Response: Overall Investigator Evaluation

Elmiron	Mean	33.9	-4.1	17.3	18.2	18.8	19.7	0.31
	Std Dev	34.8	18.8	34.8	27.6	22.2	31.1	
	n	14	6	13	11	8	52	
Placebo	Mean	17.5	16.7	10.6	9.4	14.6	13.3	
	Std Dev	29.0	25.3	21.6	16.1	10.6	21.6	
	n	10	6	13	12	4	49	

TABLE 23
COMPARISON OF PATIENT PERCEPTION OF
IMPROVEMENT WITH OTHER MEASURES OF IMPROVEMENT

<u>Response</u>	<u>Outcome</u>	<u>Overall Patient Evaluation</u>		<u>Treatment Group Comparison (p-value)</u>
		<u>Better</u>	<u>Not Better</u>	
Pain-Based on Change (1) In Rating Scale	Better	17 (85%)	18 (25%)	0.001
	Not Better	3 (15%)	55 (75%)	
Pain-Based on Patients Final Evaluation	Better	17 (85%)	4 (5%)	0.001
	Not Better	3 (15%)	77 (95%)	
Urgency-Based on Change In Rating Scale	Better	16 (73%)	27 (34%)	0.002
	Not Better	6 (27%)	52 (66%)	
Pressure-Based on Patient's Final Evaluation	Better	15 (68%)	3 (3%)	0.001
	Not Better	7 (32%)	85 (97%)	
Overall Investigator Evaluation	Better	13 (32%)	2 (2%)	0.002
	Not Better	4 (13%)	86 (97%)	
Number of Voids per day Change From Baseline to Endpoint	Mean	-4.5**	-0.1	0.004
	Std Dev	3.9	5.5	
	n	21	79	
Volume Per Void Change From Baseline to Endpoint	Mean	35.1*	1.7	0.02
	Std Dev	76.1	25.2	
	n	21	79	
Total Volume Voided Change From Baseline to Endpoint	Mean	-15.0	29.3	0.27
	Std Dev	487.5	464.4	
	n	21	79	

* Significantly different from zero, $p \leq 0.05$.

** Significantly different from zero, $p \leq 0.01$.

(1) Patients whose rating of pain at baseline (visit 0)
was zero are excluded from this analysis.

ADVERSE REACTION SUMMARY

The following table 24 describes a summary of the adverse reaction/s reported by the patients treated by Elmiron or placebo. The incidence of adverse reactions was low in those included in this study E-001.

According to this table, 54 patients were treated with Elmiron and 56 were treated with placebo. - Five patients (9%) of the 54 treated with Elmiron reported nine adverse effects with the medication, although no one was severe, some patients reported more than one reaction. Forty nine patients (91%) were free of side effects.

Among the 56 patients treated in the placebo group, 8 (14%) reported a total of 9 adverse reactions, while 48 patients (86%) were free of side effects.

TABLE 24

ADVERSE REACTION SUMMARY

<u>Patients Experiencing An Adverse Reaction</u>	<u>Elmiron</u>	<u>Placebo</u>	<u>Treatment⁽¹⁾ Group Comparison (p-value)</u>
Yes	5 (9%)	8 (14%)	0.56
No	49 (91%)	48 (86%)	

Number and Percent of Patients Experiencing An Adverse Reaction

<u>Reaction</u>	<u>Elmiron</u>	<u>Placebo</u>
Headache	1 (1.9%)	2 (3.6%)
Nausea	2 (3.8%)	0 (0.0%)
Indigestion	1 (1.9%)	0 (0.0%)
Increased Perspiration	1 (1.9%)	0 (0.0%)
Severe Mood Swings	1 (1.9%)	0 (0.0%)
Suicidal Ideation	1 (1.9%)	0 (0.0%)
Diarrhea	1 (1.9%)	2 (3.6%)
Dizziness	1 (1.9%)	0 (0.0%)
Severe Joint Pain	0 (0.0%)	1 (1.8%)
Explosive Diarrhea	0 (0.0%)	1 (1.8%)
Skin Rash on Arms	0 (0.0%)	1 (1.8%)
Itching	0 (0.0%)	1 (1.8%)
Severe Diarrhea	0 (0.0%)	1 (1.8%)

(1) Fisher's Exact test.

RESULTS OF THE LABORATORY TESTS.

Attached to this submission are tables 25 to 49. These tables are related to the results of the different blood tests and urinalysis separated by the parameters studied and the figures obtained in each of the 5 sites of investigation under the five investigators. No severe deviations from the baseline were observed.

The following is a reproduction of the sponsor's comments as appeared in page 756, Volume 1.10 (vol.10 of 20 vols.) of this submission:

"7. The change in laboratory parameters was generally small and not statistically significant. The parameters for which statistically significant treatment group differences were found or were approached are: WBC, mono, platelet, PTT, calcium, and urine creatinine. Among these six parameters, the only ones for which the mean change from baseline was statistically significant for the Elmiron group were mono and calcium. For mono the mean increase was 1.45% and for calcium the mean increase in the Elmiron treated patients was 0.19 mg%."

EXTENT OF PATIENT EXPOSURE

Duration of treatment (months)	Number of patients	
	ELMIRON	PLACEBO
3 months (Study completed)	51	47
2 months	0	1
1 month	0	2
Less than 1 month	3 (1 AE)	6 (2 AE)
Total patients	54	56

AE = Adverse Experience.

MEDICAL OFFICER'S REVIEW OF THE SECOND PROTOCOL.
Review of Vol. 1.11 (Vol. 11 of 20 vols)

BACKGROUND INFORMATION:

On October 19, 1988, this M.O. reviewed a protocol submitted on September 23, 1988 under IND which incorporated some revisions from the original one as suggested by this Division after several months of discussions, meetings, etc., etc.. The last problem was related to the proposed statistical analysis as described by the sponsor and it was solved to the satisfaction of Richard A. Stein, Ph. D., Mathematical Statistician from HFD-713 as per his memorandum dated Nov. 28, 1988.. From medical standpoint, the protocol was considered appropriate for the objective enunciated in the title by the sponsor.

TITLE OF PROTOCOL:

"AN IND PROTOCOL FOR THE EVALUATION OF ELMIRON (PENTOSAN POLYSULFATE SODIUM) IN THE TREATMENT OF THE SYMPTOMS OF INTERSTITIAL CYSTITIS"

July 13, 1988.

Protocol: E-002.

NOTE The clinical development of Elmiron was sponsored initially by _____ under IND. Later it was transferred to _____ and finally transferred again on February 28, 1991 to the current sponsor: Baker Cummins Pharmaceuticals, Inc. who are submitting these protocols E-001 and E-002 under NDA 20-193

OBJECTIVE:

"To evaluate the safety and efficacy of Elmiron, 100 mg t.i.d. compared to placebo t.i.d. in the relief of symptoms caused by documented interstitial cystitis" The study was projected to be a 3 month randomized, double blind trial with 100 to 120 patients having the syndrome of interstitial cystitis. The trial would continue on an open basis with Elmiron treatment for up to 12 months.

STUDY DESIGN:

The protocol for this study was designed as a multicentric, double-blind, placebo controlled, parallel group evaluation of Elmiron for the symptomatic treatment of patients with interstitial cystitis. Patients were randomly assigned to treatment with Elmiron or placebo in accordance with a computer generated random code. Patients were instructed to take one capsule three times a day, one hour before meals or two hours after meals.

NOTE: The main difference between this study and and first is that in the first study (E-001), the patient population was a refractory one with patients who failed previous therapy, while in this second study (E-002) failure of previous therapy was not a strict entry requirement.

For this study E-002, patients were treated in the same pattern as those treated under protocol E-001, that is, they were seen for an initial examination to document the diagnosis of interstitial cystitis, record baseline criteria of disease, and establish patient eligibility for inclusion in the study. Patients meeting all inclusion criteria were started on treatment with Elmiron or placebo and continued for a period of 3 months, after which they completed a self evaluation of the results of treatment and were evaluated by the investigator.

All patients receiving Elmiron during the three-month double-blind treatment period were given the opportunity to continue Elmiron for up to 1 year. Those patients that received placebo during the double-blind period and did not improve during those three months were started on Elmiron and had the opportunity to continue with this drug for 1 year. Patients who reported overall improvement of more than 25% were asked to wait until their symptoms recurred before starting on Elmiron for the treatment period of up to 1 year.

MATERIALS AND SUPPLIES:

Investigative drug: Elmiron tablets, 100 mg to be administered 1 tablet t.i.d.

Placebo: Tablets similar to the Elmiron, to be administered 1 tablet t.i.d.

SELECTION OF PATIENTS:

Number: This study was planned to be performed in 7 separated centers, one for each investigator. This study was projected to be performed taking in consideration the experiences and reports obtained from the study E-001. The number of patients planned for inclusion in this second proposed study-protocol was 130 to 140 patients, but the final number of patients enrolled were 151 with documented interstitial cystitis with a duration of 1 year or more.

76 patients were assigned to Elmiron

75 patients were assigned to placebo.

Three patients: 2 randomized to Elmiron, 1 assigned to placebo never started the initial treatment, for that reason the total number was reduced to 148.

9 patients in the Elmiron group failed to complete the 3-month study.
9 patients in the placebo group failed to complete the 3-month study.

Reason/s for dropping the study in the Elmiron group:

6 patients were not seen after enrollment

2 patients were not seen after the first month.

1 patient was not seen after the second month.

3 of these patients on Elmiron dropped because of adverse experiences:

1 pt. because bowel obstruction.(not related to therapy).

1 pt. because yeast infection and increased nocturia (evaluated as possibly related to therapy).

1 pt. because watery eyes, increased mole size, and rhinorrhea,(evaluated as possibly related to therapy).

- Reason/s for dropping in the placebo group:
5 pts. dropped out because the following adverse experiences
- 1 pt. because nausea, diarrhea, and running eyes (evaluated as not likely to be related to therapy).
 - 1 pt. because worsened of pain after completed month 1 (evaluated as possibly related to therapy).
 - 1 pt. during the first month because of attempted suicide (evaluated as not related to therapy).
 - 1 pt. during the first month, because of side to side eye movements (evaluated as not related to therapy).
 - 1 pt. after completing month 1 because of nausea, vomiting, diarrhea, headache, and jaundice (evaluated as not related to therapy).

The remaining patients in each group were lost to follow-up without giving a reason, all of them did not complete the 3 month evaluation period.

Final number of patients enrolled that completed the 3 month double-blind period:

- 65 patients in the Elmiron group.
 - 65 patients in the placebo group.
- (See page 1-066 ; Vol.9 of 20)

INCLUSION CRITERIA:

To be included in the study, patients had to have satisfied the following symptom complex for at least one year:

- 1) Have urgency expressed as "moderate" on the analog scale contained in the Case Report Form (Pre-treatment Report).
- 2) Have a frequency of at least 8 voids per day.
- 3) Have nocturia of at least 1-2 voids per night.
- 4) Have pain as recorded on the analog scale contained in the Case Report Form.(Pain and Urgency Scales).
- 5) Have an average voided volume per void of 50 to 200 ml measured over a 3 day period.
- 6) Have a negative urine culture and cytology.
- 7) Have a cystoscopic examination under anesthesia (80 cm of water and 1 minute distension) showing petechial hemorrhages or ulcers with gross blood in the fluid return and a bladder capacity of 350 to 1000 ml.

EXCLUSION CRITERIA:

Patients were excluded from the study if they:

- 1) Were less than 18 years of age.
- 2) Were pregnant.
- 3) Were premenopausal and not practicing effective means of birth control.
- 4) Had evidence of active bleeding peptic ulcer disease.
- 5) Had a bleeding diathesis.
- 6) Were receiving anticoagulant therapy.
- 7) Were chronic users of narcotics.
- 8) Had a known allergy to Elmiron.
- 9) Were not available for the duration of the study, for completion of follow-up examinations, or were not able to follow instructions.
- 10) Were using artificial sweeteners.
- 11) Were lactating mothers.
- 12) Showed any signs of the following:
 - a. Recurrent bacteriuria.
 - b. Obvious neurological impairment.
 - c. History of pelvic irradiation or previous treatment with known bladder irritants.
 - d. Bladder carcinoma.
 - e. Urinary TB.
 - f. Schistosomiasis.
- 13) Had been treated with Elmiron or conventional therapies within the past 4 weeks.

SITE	INVESTIGATOR	PATIENTS	
		Enrol.	Comp.
1	C. Lowell Parsons, M.D. (*) University of CA, San Diego Med. Ctr. San Diego, CA 92103	29	27
2	Phillip Hanno, M.D. (*) Hospital of the Univ. of PA Philadelphia, PA 19104	33	27
3	George Benson, M.D. 6431 Fannin Street, Houston, Texas 77031	9	8
4	Stacy J. Childs, M.D. Brookwood Ambulatory Care Ctr. 2022 Brookwood Med. Ctr. D Birmingham, Alabama 35209	32	28
5	Suzanne Frye, M.D. 15 Park Ave New York, N.Y. 10016	8	8
6	George Webster, M.D. Duke Univ. Med. School, Box 3146 Durham, N.C. 27710	14	13
7	Grannum R. Sant, M.D. (*) Tufts Univ. School of Medicine Boston, MA 02111	23	19
Total Patients		148	130

Drs. Parsons, Hanno, and Sant were investigators to study E-001. (*)
Drs. Parsons, Hanno, and Sant are qualified to be investigators to
this NDA as per their C.V. submitted previously with study E-001.

C.V. of Drs. Benson, Childs, Frye, Webster, and Sant were not
submitted by the sponsor.

STUDY MONITOR:

James T. Baldini, Ph.D.
Medical Market Specialties, Inc.,
P.O. Box 150
Boonton, New Jersey 07005

STUDY EVALUATION:

Attached to this protocol E-002 are samples of the different forms that were completed by the investigators and/or the patients before the initiation of the study to assure fulfillment of the conditions of inclusion and exclusion. Forms were also completed by the patient and/or the investigators at the initiation of the 3-month double blind treatment, every month during the course of the treatment and at the end of the third month at which time the double-blind period of treatment ended.

These forms are the same as those used in study E-001 and are reproduced and described in the attached review of that study-protocol. For that reason there is no need to have a description of them again. The forms are the following:

- Flow sheet.
- Patient history form.
- Initial questionnaire.
- Pretreatment report (1)
- Pretreatment report (2) - Cystoscopic evaluation.
- Volume voiding profile.
- Pain and urgency scales.
- Laboratory reports
- Drug use record form.
- Follow-up questionnaire (Patient's assessment of overall improvement).
- Report of Adverse reactions.
- Investigator's Evaluation of Overall Improvement.

EXAMINATION REQUIREMENTS:

- a) All patients completed the Initial Questionnaire, the Initial Pain and Urgency analog scales, the Micturitional Profile, and have documented 8 to 24 voids per day during waking hours and an average voided bladder volume of 50 to 200 ml (3 days).
- b) Urinalysis and negative urine culture and cytology.
- c) Cystoscopic examination under anesthesia by the investigator (80 cm of water and 1 minute distension) showing petechial hemorrhages or ulcers with gross blood in the fluid return and a bladder capacity between 350 and 1000 ml. No patient was evaluated for entry until at least 6 weeks after cystoscopy. This waiting period was necessary because the dilation of the urethra by the cystoscope and/or the hydrodistension of the bladder produced by the water used for the cystoscopic examination may have induced disease remission. If the patient have been relieved of symptoms during these six weeks, he/she should be excluded from the study. If symptoms recurred the patient could be included in the study. Once the test treatment was initiated, the patient should not have taken any medications that may modify bladder function or have been treated by any of the conventional methods of treatment for this disease e.g. local urethral and/or bladder treatments.
- d) Biopsy was not required.
- e) Cystometrograms were optional.

CRITERIA FOR DETERMINING EFFICACY:

For this study-protocol E-002, the variables for the determination of Elmiron efficacy in order of relevancy were:

- The patient's assessment of overall improvement.
- The investigator's assessment of overall improvement.
- The change in pain and urgency.
- The change in nocturia
- The change in frequency
- The change in average voided volume.

In each case, the change from the baseline values to the values at the end of the double blind period was used as the basis for determining efficacy. All patients were seen at 0 time before start of treatment for baseline symptom measurements and laboratory values and at 12 weeks (3 months) after start of treatment for measurement of these same variables

CRITERIA FOR DETERMINING SAFETY:

Safety assessment was based on the occurrence of adverse reactions during the period of administration of Elmiron as well as the comparison of laboratory data between baseline and at the endpoint of the study.

RESULTS OF THIS STUDY.

PRIMARY EFFICACY VARIABLES (Patient's assessment of Overall Improvement):

The primary efficacy variables were recorded at the end of the 3-month double blind period and compared to the symptoms recorded at baseline.

First primary efficacy variables:

The number and/or percentage of patients evaluating their degree of OVERALL IMPROVEMENT was the first of the 3 primary variables for determining the effectiveness of Elmiron. A form was completed by the patient at the end of the third month of double-blind treatment. This form is attached to this submission as "Exhibit 1" under the title: "Follow-up questionnaire: complete at the end of 3-months double-blind period"

In that form, patients circled the categories which best described the OVERALL CHANGE IN PAIN, URGENCY, QUALITY OF LIFE and OVERALL CHANGE IN THEIR INTERSTITIAL CYSTITIS by comparing those parameters to same factors before they started the treatment.

Patients rated the changes in the above variables as:

- Worse
- No better.....0%
- Slightly Improved.....25%
- Moderately Improved.....50%
- Greatly Improved.....75%
- Symptoms Gone.....100%

SECOND PRIMARY EFFICACY VARIABLES (Pain and Urgency Scale Data):

The PAIN and URGENCY SCALE DATA was considered the second of the 3 primary variables for comparative analysis of Elmiron and placebo. A form was completed by the patients at the end of the third month of treatment. This form is attached to this submission as "Exhibit 2" under the title "Elmiron in interstitial cystitis. Pain and Urgency scales" Patients circled in these scales the number that best described their bladder pain and their urgency to urinate.

Scale one was related to Pain with numbers 0 to 5 as None, Mild, Moderate and Severe, were None = 0
 Mild = 1
 Moderate = 3
 Severe = 5

Scale two was related to Urgency with numbers 0 to 5 as None, Mild, Moderate and Severe, were None = 0
 Mild = 1
 Moderate = 3
 Severe = 5

THIRD PRIMARY EFFICACY VARIABLES (Investigator's Evaluation of overall Improvement).

The third of the 3 primary variables for analysis was the INVESTIGATOR'S EVALUATION OF OVERALL IMPROVEMENT as indicated by the % of patients evaluated as having an overall improvement of more than 25%. A form was completed by the investigator attached to this submission as "Exhibit 3" under the title "Investigator's Evaluation of Overall Improvement". In this form the investigator circled the number that best described his opinion of Patient's Overall Improvement at End of the 3-month Study.

The investigator rated his opinion under the following classification:
 WORSE: Patient's symptoms generally more severe than at start of study
 NO CHANGE: Patient's symptoms essentially unchanged since start.
 FAIR: About 25% improvement in one or more symptoms.
 GOOD: About 50% improvement in two or more symptoms.
 VERY GOOD: About 75% improvement in two or more symptoms.
 EXCELLENT: About 100% improvement in essentially all symptoms

NOTE: REPRODUCTIONS OF THESE THREE FORMS ARE ATTACHED TO THIS REVIEW IN THE FOLLOWING PAGES.

Exhibit :

FOLLOW-UP QUESTIONNAIRE: COMPLETE AT END OF 3-MONTHS DOUBLE-BLIND PERIOD

NAME: _____

DATE: _____

PATIENT NO. _____

(Please circle the category that BEST describes your condition TODAY in COMPARISON to your condition BEFORE you started this treatment. Also fill in the number where called for.)

1. Please circle the category below that you think best describes the OVERALL change in the PAIN associated with your bladder since the start of therapy

a) worse	-
b) no better	(0%)
c) slightly improved	(25%)
d) moderately improved	(50%)
e) greatly improved	(75%)
f) symptom gone	(100%)

2. Please circle the category below that you think best describes the OVERALL change in the URGENCY or pressure to urinate associated with your disease since the start of therapy

a) worse	-
b) no better	(0%)
c) slightly improved	(25%)
d) moderately improved	(50%)
e) greatly improved	(75%)
f) symptom gone	(100%)

3. Do you have and enjoy sexual intercourse more now than before the start of therapy? YES NO

4. How often do you get up at night to urinate? _____ times

5. Do you get a better night's sleep now than before the treatment started? YES NO

6. Considering your responses to items 1 to 5, please circle the category below that best describes the OVERALL CHANGE in your interstitial cystitis COMPARED TO BEFORE YOU STARTED TREATMENT.

a) worse	-
b) no better	(0%)
c) slightly improved	(25%)
d) moderately improved	(50%)
e) greatly improved	(75%)
f) symptoms gone	(100%)

Exhibit 2

ELMIRON IN INTERSTITIAL CYSTITIS.

PAIN & URGENCY SCALES

INVESTIGATOR: _____ DATE: _____

PATIENT NAME: _____ PATIENT NO.: _____

TREATMENT MONTH: 0 1 2 3 6 9 12

SCALE ONE PAIN

NONE MILD MODERATE SEVERE
 0 1 2 3 4 5

1. Please rate by circling on Scale One above the number that BEST DESCRIBES THE BLADDER PAIN, if any, you have GENERALLY HAD DURING THE PAST MONTH

SCALE TWO URGENCY (URINARY PRESSURE TO URINATE)

NONE MILD MODERATE SEVERE
 0 1 2 3 4 5

2. Please rate by circling on Scale Two above the number that BEST DESCRIBES THE URINARY PRESSURE OR URGENCY, if any, you have GENERALLY HAD DURING THE PAST MONTH.

Exhibit 3

INVESTIGATOR'S EVALUATION OF OVERALL IMPROVEMENT

INVESTIGATOR _____ DATE _____

PATIENT NAME _____ PATIENT NO. _____

(Circle number that best describes your opinion of patient's overall improvement at end of 3-month study)

1. WORSE: patient's symptoms generally more severe than at start of study
2. NO CHANGE: patient's symptoms essentially unchanged since start of study
3. FAIR: about 25% improvement in one or more symptoms
4. GOOD: about 50% improvement in two or more symptoms
5. VERY GOOD: about 75% improvement in two or more symptoms
6. EXCELLENT: about 100% improvement in essentially all symptoms

RESULTS OF THIS STUDY.

The following are excerpts from tables 1 to 46, pages 5-1198 through 5-1279G from Vol. 11 of 20 vols. as submitted by the sponsor.

SELECTION OF PATIENTS

Number:

As described in pages 43 and 44 of this review, although originally the number of patients planned to be enrolled in this study was 151 with documented interstitial cystitis with a duration of 1 year or more, three patients (2 randomized to Elmiron and 1 randomized to placebo) never started the initial treatment. For that reason the number was reduced to 148. Due to the reasons explained by the sponsor, (see pages 43 and 44 of this review) the total number of patients that completed the 3-month double blind period was later reduced to 130.

Final number of patients:

- 65 patients randomized to the Elmiron group.
- 65 patients randomized to the placebo group.

Number of patients treated in each site:

Group	SITE							COMBINED NUMBER
	1	2	3	4	5	6	7	
Elmiron	15	16	5	16	4	6	12	74
Placebo	14	17	4	16	4	8	11	74
<u>Sex</u>								
Elmiron Male	0	0	0	0	0	0	0	0 (0%)
Female	15	16	5	16	4	6	12	74 (100%)
Placebo Male	2	0	1	1	0	0	1	5 (7%)
Female	12	17	3	15	4	8	10	69 (93%)
<u>Duration of disease (years)</u>								
Elmiron	15	16	5	16	4	6	12	74
Placebo	13	17	4	15	4	7	11	71

PAIN SUMMARY:

The sponsor enclosed in tables 4 through 6 a summary of the pain data at baseline, at month 3, and at endpoint. (mean combined figures from the 7 sites of study).

Table 4 displays a summary of the rating of pain (0=none to 5=severe) at months 0, 3, and at endpoint.

Table 5 summarizes the change of pain from baseline (month 0) to month 3 and to end point.

Table 6 summarizes improvement of pain from baseline (month 0) to month 3 and to end point. A patient is better if there is an improvement of at least one on the analog pain scale.

Results:

Table 4: Rate of pain at month 0 and at endpoint of treatment as follows: 0=none--5=severe, mean combined figures at the seven sites:

GROUP	RATING OF PAIN AT MONTH 0	RATING OF PAIN AT ENDPOINT
Elmiron	(74 patients)...3.6	(68 patients)...2.6
Placebo	(74 patients)...3.5	(68 patients)...2.6

No statistically significant treatment group differences were found.

Table 5: Change of pain from baseline to endpoint. Mean combined figures at the seven sites of investigation:

GROUP	AT MONTH 3	AT ENDPOINT
Elmiron	-1.1	-1.0
Placebo	-0.8	-0.8

No statistically significant treatment group differences were found.

Table 6: Patient improvement in pain (a patient is better if there is an improvement of at least one on the analog pain scale). Combined figures and % at the seven sites of investigation:

GROUP	AT MONTH 3	AT ENDPOINT
Elmiron	Improved 42 pts (66%)	Improved 43 pts (63%)
	Not improved 22 pts (34%)	Not improved 25 pts (37%)

Placebo	Improved 33 pts (51%)	Improved 34 pts (50%)
	Not improved 32 pts (49%)	Not improved 34 pts (50%)

No statistically significant treatment group differences were found.

URGENCY SUMMARY:

The Urgency data was recorded on a monthly basis and summarized in tables 7 through 9.

Table 7 displays a summary of the rating of urgency (0=none to 5=severe) at months 0, 3, and at endpoint.

Table 8 summarizes the change of urgency from baseline (month 0) to the third month and to endpoint.

Table 9 summarizes patient improvement in urgency from baseline (month 0) to month 3 and at endpoint (a patient is better if there is an improvement of at least one on the analog urgency scale).

Results:

Table 7. Rate of urgency at month 0, at month 3 and at the endpoint. Mean combined figures from the 7 sites of investigation.

GROUP	AT MONTH 0	AT MONTH 3	AT ENDPOINT
Elmiron	(74 patients) 4.0	(64 pts) 2.9	(68 pts) 2.9
Placebo	(74 patients) 4.0	(65 pts) 3.2	(68 pts) 3.2

No statistically significant treatment group differences were found.

Table 8: Change of urgency from baseline to month 3 and at endpoint. Mean combined figures at the seven sites of investigation

GROUP	AT MONTH 3	AT ENDPOINT.
Elmiron	(64 patients) -1.0	(68 patients) -1.0
Placebo	(65 patients) -0.9	(68 patients) -0.8

No statistically significant treatment group differences were found.

Table 9: Patient improvement in urgency from baseline (month 0) to month 3 and at endpoint. (a patient is better if there is an improvement of at least one on the analog urgency scale). Combined figures and % at the seven sites of investigation.

GROUP	AT MONTH 3	AT ENDPOINT
Elmiron	Improved 39 pts (61%)	42 patients (62%)
	Not improved 25 pts. (39%)	26 patients (38%)
Placebo	Improved 28 pts (43%)	29 patients (43%)
	Not improved 37 pts (57%)	39 patients (57%)

Statistically significant treatment group differences were found at both month 3 and at endpoint.

VOIDING PROFILE DATA:

Voiding profile data were collected for each patient for a 3 day period of the time associated with each of the monthly visits (0, 1, 2, 3). In the tables attached by the sponsor, the data is referred only to months 0, 3, and endpoint, and they are summarized in tables 10 through 19.

Tables 10 through 12 display a summary of the voids per day (24 hours).

Table 10 displays a summary of the voids per day at each month (0 and 3) and at endpoint.

Table 11 summarizes the change of number of voids per 24 hours from baseline (month 0) to month 3 and at endpoint.

Table 12 displays the patient improvement in voids per day (24 hours) at month 3 and at endpoint. A patient is better if there is at least a reduction of 3 voids per day.

Table 13 displays a summary of the voids per night at months 0, 3, and at endpoint.

Table 14 summarizes the changes of number of voids per night from baseline (month 0) to month 3 and at endpoint.

Table 15 displays a summary of the volume per void at months 0, 3, and at endpoint.

Table 16 summarizes the changes of the volume per void (c.c.) from baseline (month 0) to month 3 and at endpoint.

Table 17 summarizes the patient improvement in volume per void from baseline to month 3, and at endpoint. (a patient is better if there is at least a 20 c.c. increase in volume per void).

Table 18 summarizes the daytime volume of void at months 0, 3, and at endpoint

Table 19 summarizes the change of the total volume voided (cc) from baseline (month 0) to month 3 and at endpoint.

RESULTS OF THE VOIDING PROFILE DATA:

Table 10: Summary of the number of voids per day (24 hours) at baseline (month 0), at month 3, and at endpoint. Mean combined figures from the 7 sites of investigation.

GROUP	AT MONTH 0	AT MONTH 3	AT ENDPOINT
Elmiron	(73 patients) 17.9	(63 pts) 16.2	(67 pts) 16.6
Placebo	(74 patients) 18.4	(64 pts) 16.9	(67 pts) 16.8

No statistically significant treatment group differences were found.

Table 11: Change of number of voids per 24 hours from baseline (month 0) to month 3 and at endpoint. Mean combined number from the 7 sites of investigation.

GROUP	AT MONTH 3	AT ENDPOINT
Elmiron	(62 patients) -1.8	(66 pts) -1.6
Placebo	(64 patients) -2.1	(67 pts) -2.1

No statistically significant treatment group differences were found.

Table 12: Patient improvement in voids per day (24 hours) from baseline to month 3 and at endpoint. A patient is better if there is at least a reduction of 3 voids per day. Combined figures and % from the 7 sites

GROUP	AT MONTH 3	AT ENDPOINT
Elmiron	<u>Improved</u> 23 pts. (37%)	24 pts. (36%)
	<u>Not improved</u> 39 pts. (63%)	42 pts. (64%)
Placebo	<u>Improved</u> 27 pts. (42%)	28 pts. (42%)
	<u>Not improved</u> 37 pts. (58%)	39 pts. (58%)

No statistically significant treatment group differences were found.

Table 13: Summary of the number of voids per night at baseline (month 0), at month 3 and at endpoint. Mean combined figures from the 7 sites.

GROUP	AT MONTH 0	AT MONTH 3	AT ENDPOINT
Elmiron	(71 patients) 4.4	(61 pts) 3.7	(65 pts) 3.9
Placebo	(74 patients) 3.8	(64 pts) 3.1	(67 pts) 3.2

No statistically significant treatment group differences were found.

Table 14: Change of number of voids per night from baseline (month 0) to month 3 and at endpoint. Mean combined figures from the 7 sites.

GROUP	MONTH 3	AT ENDPOINT
Elmiron	(58 patients) -0.5	(62 pts) -0.3
Placebo	(64 patients) -0.8	(67 pts) -0.8

No statistically significant treatment group difference was found.

Table 15: Summary of the volume per void (c.c.) at month 0, at month 3 and at endpoint.- Mean combined figures from the 7 sites.

GROUP	AT MONTH 0	AT MONTH 3	AT ENDPOINT
Elmiron	(73 patients) 99.6	(63 pts) 119.9	(67 pts) 120.8
Placebo	(74 patients) 100.6	(63 pts) 111.2	(66 pts) 110.9

No statistically significant treatment group differences was found.

Table 16: Changes of the volume per void (c.c.) from baseline (month 0) to month 3 and at endpoint. Mean combined figures from the 7 sites.

GROUP	AT MONTH 3	AT ENDPOINT
Elmiron	(62 patients) 19.7	(66 pts) 20.4
Placebo	(63 patients) 12.0	(66 pts) -2.1

No statistically significant treatment group differences was found .

Table 17: Patient improvement in volume per void from baseline to month 3 and at endpoint (a patient is better if there is at least a 20 c.c. increase in volume per void). Combined figures from the 7 sites and percent.

GROUP	AT MONTH 3	AT ENDPOINT.
Elmiron	Improved 25 pts (40%)	Improved 26 pts (39%)
	Not improved 37 pts (60%)	Not improved 40 pts (61%)
Placebo (24%)	Improved 15 pts (24%)	Improved 16 pts
	Not improved 48 pts (76%)	Not improved 50 pts (76%)

A statistically significant treatment group difference was found at month 3.

Table 18: Total daytime volume of void(c.c.) at months 0 (baseline), 3 and at endpoint. Mean combined figures from the 7 sites of investigation.

GROUP	AT MONTH 0	AT MONTH 3	AT ENDPOINT
Elmiron	(73 patients) 1340.5	(63 pts) 1345.7	(67 pts) 1367.2
Placebo	(74 patients) 1347.6	(63 pts) 1339.7	(66 pts) 1321.7

No statistically significant treatment group differences were found.

Table 19: Change of total daytime volume voided (c.c.) from baseline (month 0) to month 3 and at endpoint. Mean combined figures from the 7 sites of investigation.

GROUP	AT MONTH 3	AT ENDPOINT
Elmiron	(62 patients) -7.5	(66 pts) 3.3
Placebo	(63 patients) -29.6	(66 pts) -42.0

No statistically significant treatment group differences were found.

RESULTS OF THE OVERALL EVALUATIONS OF EFFICACY:

Tables 20 and 21 summarize the analysis of the overall evaluations of efficacy.

In table 20 the following parameters were evaluated:

- a) Response: Pain based on change in rating scale.
- b) Response: Pain based on Patient's Final Evaluation
- c) Response: Urgency-based on change in rating scale
- d) Response: Urgency-based on Patient's Final Evaluation
- e) Response: Overall Patient Evaluation
- f) Response: Overall Investigator Evaluation
- g) Response: Enjoy Sexual Intercourse more
- h) Response: Do you get a Better Night's Sleep?

In table 21 the following parameters were evaluated related to Primary Efficacy Measures--Percent Improvement.:

- a) Response: Pain
- b) Response: Urgency
- c) Response: Overall Patient Evaluation
- d) Response: Overall Investigator Evaluation

Table 20: Overall evaluation summary.

Summary of Percent of Patients Improved in the 7 sites

- a) Response: Pain based on change in rating scale.
Combined and percent figures.

GROUP	OUTCOME	COMBINED AND PERCENT
Elmiron	Better	43 patients (63%)
	Not better	25 patients (37%)
Placebo	Better	34 patients (52%)
	Not better	32 patients (48%)

No statistically significant treatment group differences were found.

NOTE: Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis. (See this M.O.'s comments about this matter)

Table 20 (Cont'd).

b) Response: Pain Based on Patient's Final Examination
 Combined and percent figures.

Elmiron	Better	28 (38%)
	Not Better	46 (62%)
Placebo	Better	13 (18%)
	Not better	59 (82%)

Statistically significant treatment group differences were found.

NOTE: Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis.

c) Response: Urgency-Based on Change in Rating Scale
 Combined percent figures

Elmiron	Better	42 (62%)
	Not Better	26 (38%)
Placebo	Better	29 (43%)
	Not Better	39 (57%)

Statistically significant treatment group differences were found.

d) Response: Urgency-Based on Patient's Final Evaluation.
 Combined percent figures

Elmiron	Better	22 (30%)
	Not Better	52 (70%)
Placebo	Better	13 (18%)
	Not Better	61 (82%)

Statistically significant treatment group differences were found.

e) Response: Overall Patient Evaluation

Elmiron	Better	24 (32%)
	Not Better	50 (68%)
Placebo	Better	12 (16%)
	Not Better	62 (84%)

Statistically significant treatment group differences were found.

Table 20 (Cont'd).

Overall Evaluation Summary.
Summary of Percent of Patients Improved.

f) Response: Overall Investigator Evaluation.

Elmiron	Better	27 (36%)
	Not Better	47 (64%)
Placebo	Better	11 (15%)
	Not Better	63 (85%)

Statistically significant treatment group differences were found.

g) Response: Enjoy Sexual Intercourse More.

Elmiron	Yes	15 (31%)
	No	34 (69%)
Placebo	Yes	10 (18%)
	No	46 (82%)

No statistically significant treatment group differences were found.

h) Response: Do You Get A Better Night's Sleep?

Elmiron	Yes	27 (41%)
	No	39 (59%)
Placebo	Yes	25 (39%)
	No	39 (61%)

No statistically significant treatment group differences were found.

Table 21: In table 21 the following parameters were evaluated related to Primary Efficacy Measures. Percent Improvement. All were in mean, combined figures in the seven sites of investigation.

- a) Response: Pain
- b) Response: Urgency
- c) Overall Patient Evaluation
- d) Overall Investigator Evaluation.

a) Response: Pain Percent Improvement

GROUP	MEAN, COMBINED PERCENT
Elmiron	67 patients (30.4%)
Placebo	64 patients (18.2%)

Statistically significant treatment group differences were found.

b) Response: Urgency Percent Improvement.

Elmiron	66 patients (25.8%)
Placebo	65 patients (15.2%)

Statistically significant treatment group differences were found.

c) Response: Overall Patient Evaluation Improvement.

Elmiron	67 patients (28.7%)
Placebo	65 patients (16.5%)

Statistically significant treatment group differences were found.

d) Response: Overall Investigator Evaluation Improvement.

Elmiron	68 patients (28.9%)
Placebo	67 patients (15.7%)

Statistically significant treatment group differences were found.

Table 22 This table compares the patient's perception of overall improvement (better or no better) with the other primary measures of efficacy.

TABLE 22

COMPARISON OF PATIENT PERCEPTION OF
IMPROVEMENT WITH OTHER MEASURES OF IMPROVEMENT

<u>Response</u>	<u>Outcome</u>	<u>Overall Patient Evaluation</u>		<u>Treatment Group Comparison (p-value)</u>
		<u>Better</u>	<u>Not Better</u>	
Pain-Based on Change ⁽²⁾ In Rating Scale	Better	29(81%)	48(49%)	0.001
	Not Better	7(19%)	50(51%)	
	Better			
Pain-Based on ⁽²⁾ Patient's Final Evaluation	Better	36(100%)	5(5%)	<0.001
	Not Better	0(0%)	105(95%)	
	Better			
Urgency-Based on Change In Rating Scale	Better	33(92%)	38(38%)	<0.001
	Not Better	3(8%)	62(62%)	
	Better			
Urgency-Based on Patient's Final Evaluation	Better	32(89%)	3(3%)	<0.001
	Not Better	4(11%)	109(97%)	
	Better			
Overall Investigator Evaluation	Better	34(94%)	4(4%)	<0.001
	Not Better	2(6%)	108(96%)	
	Better			
Number of Voids Per Day Change From Baseline to Endpoint	Mean	-4.9 ^{**}	-0.8	0.0002
	Std Dev	4.3	5.3	
	n	36	96	
Volume Per Void Change From Baseline to Endpoint	Mean	37.4 ^{**}	7.5	0.01
	Std Dev	55.8	40.7	
	n	36	96	
Total Volume Voided Change From Baseline to Endpoint	Mean	-56.4	-5.5	0.42
	Std Dev	368.3	568.5	
	n	36	96	

** Significantly different from zero, $p \leq 0.01$.

(1) Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis.

Table 23: Adverse Reaction Summary.

Among the 74 Elmiron treated patients, 7 (9%) reported a total of 12 adverse reactions. Among the 74 placebo patients, 10 (14%) reported a total of 19 adverse reactions. Within the treatment group only nausea, diarrhea and vomiting occurred in more than one patient. For the placebo group three patients reported nausea and two reported diarrhea and vomiting

Adverse Reaction	Elmiron	Placebo
Yes	7 (9%)	10 (14%)
No	67 (91%)	64 (86%)

Table 24: Adverse Reaction Summary.

Number and percent of patients experiencing individual Adverse Reactions.

TABLE 24

**ADVERSE REACTION SUMMARY
NUMBER AND PERCENT OF PATIENTS EXPERIENCING
INDIVIDUAL ADVERSE REACTIONS**

<u>Reaction</u>	<u>Elmiron</u>	<u>Placebo</u>
Nausea	1 (1.4%)	3 (4.1%)
Diarrhea	1 (1.4%)	2 (2.7%)
Amenorrhea	0 (0%)	1 (1.4%)
Bowel Obstruction	1 (1.4%)	0 (0%)
Cannot Sleep	1 (1.4%)	0 (0%)
Dry Nasal Mucosa	0 (0%)	1 (1.4%)
Felt "Speedy"	1 (1.4%)	0 (0%)
Headache	0 (0%)	1 (1.4%)
"High" Feeling	0 (0%)	1 (1.4%)
Increased Mole Size	1 (1.4%)	0 (0%)
Jaundice	0 (0%)	1 (1.4%)
Nocturnal Frequency	1 (1.4%)	0 (0%)
Pain Worse	0 (0%)	1 (1.4%)
Fatigued	0 (0%)	1 (1.4%)
Rash	0 (0%)	1 (1.4%)
Rhinorrhea	1 (1.4%)	0 (0%)
Runny Eyes	0 (0%)	1 (1.4%)
Side-to-Side Eye Movements	0 (0.0%)	1 (1.4%)
Soft Stools	1 (1.4%)	0 (0%)
Suicide Attempt	0 (0.0%)	1 (1.4%)
Urgency	1 (1.4%)	0 (0%)
Vaginal Itch	0 (0%)	1 (1.4%)
Vaginal Yeast Infection	1 (1.4%)	0 (0%)
Vomiting	0 (0%)	2 (2.7%)
Watery Eyes	1 (1.4%)	0 (0%)

No statistically significant treatment group difference was found.

Tables 25 through 46. Summary of Laboratory data:

The Laboratory data is summarized in tables 25 through 46. The first 7 tables display the results of Laboratory tests of C.B.C., Blood chemistries and urinalysis in the upper and lower limits reported by each of the investigators in their respective 7 study-sites.

The only parameters that showed some statistically significant treatment group differences occurred for PTT and for Calcium. These changes although observed in these two Laboratory tests were not of clinical importance or severity.

Among the remaining parameters no other mean changes from baseline were found clinically, medically or statistically significant for either treatment group.

LONG-TERM ADVERSE EFFECTS:

In this submission there are not described many adverse reactions related to the administration of Elmiron; those reported may be considered without severe clinical significance. In relation to the experience after treating patients for longer periods of time the sponsor stated that the best evidence is by following those patients who continued treatment for 2 years in Study E-001, and those patients in study E-002 who continued therapy for 1 year.

The sponsor describes that 69 patients completed 1 to 2 years of Elmiron therapy in study E-001, and as of June 15, 1990 there was 1 report of adverse event. This was a report of 3 episodes "during month 6, of mild skin swelling over left collar bone and left ankle. The patient's blood tests were all normal and she continued therapy for 1 more month without recurrence before she discontinued medication for lack of sufficient efficacy".

There is reference that from 73 patients who completed 9 to 15 months on Elmiron as June 15, 1990 in study E-002 there were 3 reports of adverse experience: one patient had back and bladder pain and urgency, this was considered as disease flare-up. The relation to therapy was not given and the patient completed 12 months of follow-up therapy. The second adverse experience was reported by a patient which completed the 6th month of therapy who complained of itching of the palms and soles without rash which was controlled by Benadryl. Patient completed the 12 month therapy. A third patient after 9 months on Elmiron reported migratory myalgias as of March 1990. Elmiron was discontinued in May 1990, but still has some muscle soreness in her legs. The only positive finding was a "persistent elevated sedimentation rate and the cause of event could not be established. The relation of the event to Elmiron was evaluated as not likely. This experience of 4 reports from 142 patients on therapy with Elmiron for up to 2 years results in an incidence of adverse events of 3%".

COMPASSIONATE USE STUDY
CONDUCTED BY

The sponsor submits in this volume 1.12 (Vol. 12 of 20 vols.) a description of the "Compassionate Open Label study" to make Elmiron available to interstitial cystitis patients, as requested by their physicians.

BACKGROUND INFORMATION:

This office received several requests from physicians for individual assignment of an IND for the compassionate treatment of patients diagnosed as suffering interstitial cystitis without relief from previous medications. It is impossible to have a complete list of the number of patients treated under this specific program. The following is a reproduction of a paragraph related to this matter from that volume.

"During the period from 1986 when the study was transferred from the previous holder of IND until March 15, 1991, physicians enrolled 1274 patients into this study. As of March 15, 1991, 630 patients were on active therapy for periods of time ranging to more than 5 years. The length of time on Elmiron is not entirely precise because it is known that some patients have been enrolled in the study after having been on Elmiron previously obtained from foreign sources or having been in other clinical studies".

In another paragraph it is stated by the sponsor that: "Until the early part of 1989, efficacy data, other than pain and urgency scales were not collected because the study was open and because it was assumed that patients would continue on therapy as long as they felt that therapy was effective. It was noted however, that some patients discontinued participation in the study for a variety of reasons other than lack of efficacy. Some switched to other sources of Elmiron to escape the 3 month examination periods; some discontinued for financial reasons, others stopped to see if they could maintain improvement without therapy; and some stopped because of adverse events. Consequently, beginning in 1989, a follow-up questionnaire was used at each 3 month period to measure the patient's evaluation of efficacy. Although the sponsor is aware of the deficiencies of open label efficacy data, it is interesting to note that of the 1274 patients enrolled in the Compassionate Use Study, 497 (39%) have completed 3 or more 3-month periods of the study, a level of continuation of therapy which corresponds to the levels of continuation of therapy seen in the well-controlled, double-blind studies E-001 and E-002".

Although the sponsor describes some details related to the 497 patients that completed 2 or more study periods as of March/1991, the data presented is weak and not very conclusive in relation to the symptoms evaluated: number of daytime voids, the number of night voids (nocturia), and the pain/discomfort score on the 10-point scale at baseline and at the last period completed.

The most common adverse reactions reported by patients were related to gastrointestinal tract, including nausea, vomiting, and diarrhea. The second most common adverse events were skin/appendages and consisted of skin rash and hair loss or thinning. Some patients complained of headaches.

Review of this study-protocol:

"A TREATMENT IND PROTOCOL FOR THE COMPASSIONATE USE OF ELMIRON (PENTOSAM POLYSULFATE SODIUM) FOR PATIENTS WITH RECURRING SYMPTOMS OF INTERSTITIAL CYSTITIS."

Protocol: CE-001.

November 1989

OBJECTIVE:

The objective of this open study was to determine the efficacy of Elmiron in relieving symptoms in patients who have been diagnosed as having interstitial cystitis.

INCLUSION CRITERIA:

All male and female patients previously diagnosed as suffering from interstitial cystitis.

EXCLUSION CRITERIA:

- a) Patients less than 18 years of age.
- b) Pregnancy.
- c) Lactating mothers.
- d) Premenopausal women not practicing birth control.
- e) Evidence of peptic ulcer.
- f) Documented bleeding disorder.
- g) Patients receiving anticoagulant therapy.
- h) Evidence of, or diagnosed as being osteoporotic.
- i) Known allergy to pentosan polysulfate sodium.
- j) Unavailable for completion of follow-up examinations or not able to follow instructions given.

ELMIRON DOSAGE FORM:

Oral capsules 100 mg. each, 1 capsule three times per day.

PRE-STUDY INVESTIGATIONS:

General medical history.
Current medications
Assessment of interstitial cystitis condition
Pain/discomfort score using analog pain scale.
Subjective symptom evaluation.
Complete blood count, prothrombin time, PTT.
Urinary pregnancy test (premenopausal women)
Urinalysis.
Urine culture and sensitivity
Voiding profile (72 hr).

NOTE: Attached to this submission the sponsor included several forms to be completed by the investigator and/or the patients related to the above pre-study investigations as well as questionnaires to be completed at end of 3-month follow-up periods. The forms submitted were samples; no individual Case Report Forms with patient's name, no investigator's findings, no physician's or patient's comments and no follow-up or conclusions were enclosed.

TREATMENT PLAN:

According to the design of this proposed study-protocol, patients should be seen and assessed regarding safety and efficacy every three months. During those visits a detailed symptom evaluation was to be recorded by the investigator and/or the patients.

NOTE: Although the investigators were supposed to submit to us the Progress Reports of patients treated under this specific program, the great majority of them failed to do it. (See this M.O.'s comments at the end of the review of this Compassionate study)

All patients received a three months supply of Elmiron.

INVESTIGATORS:

The sponsor includes in this submission a list of the names of 450 investigators that have been treating patients under this compassionate protocol. That number of physicians cannot be traced in our Division. When this compassionate program was initiated, we started receiving requests for individual IND assignment by many physicians throughout the U.S. As this was a very complicated system, and as all of them were "supposed" to follow a standard and unified study-protocol, we requested the sponsor to ask all the physicians involved in this program to withdraw their personal IND's and to include their treatment under only one IND which was the original for this drug: IND Some physicians followed the instructions from the sponsor and requested discontinuation of their IND's, but, unfortunately, a great number of them failed to comply with that request.

Another problem observed with this list is the fact that some investigators had their "own" IND for indications for Elmiron other than for the interstitial cystitis; for example, Dr. Lowell Parsons whose name is in the list submitted by Baker Cummins, has an IND for the treatment with Elmiron of patients suffering Post-Radiation proctitis in addition to having the same medication for the treatment of the symptoms of Interstitial Cystitis orally, as a bladder irrigation solution as well as by subcutaneous injections.

The number and names of physicians involved in this program registered in our computer list is only 81, but, again, this discrepancy of number could be related to the above difficult factors.

MEDICAL OFFICER'S COMMENTS:

Taking in consideration that this compassionate program was designed as an open uncontrolled study, and as stated above, the majority of investigators failed to send us the progress reports of the patients treated, and that no detailed tables, conclusions, etc., were received in this Division, it is the opinion of this M.O. that the only benefit that could be obtained from this study may be in relation to some details regarding safety, but no definitive conclusions concerning efficacy may be drawn.

OTHER DOUBLE-BLIND CLINICAL STUDIES.

1. C.L. Parsons & S.G. Mulholland: "Successful therapy of interstitial cystitis with pentosanpolysulfate" J. Urology, 138:513, 1987.

The authors studied the effects of pentosanpolysulfate in the management of symptoms of interstitial cystitis. This was a double-blind, placebo controlled, crossover study. In order to be included in this study, patients had to have at least 1 year of symptoms consisting of urgency, frequency, nocturia and/or pain. It was also required to have negative urine cultures, a cystoscopic examination showing an ulcer or petechial hemorrhage after bladder distension, biopsy proved inflammation, and negative cytology studies. A baseline questionnaire was established with the degree of urgency, frequency, nocturia and pain, and a 3-day voiding profile was completed in all the patients.

Patients graded improvements in each of their symptoms as 0, 25, 50, 75, or 100%. The dose administered was 100 mg 3 times a day in one center, and 200 mg 2 times a day at the other center. Patients were randomized to the drug or placebo and treated for 3 months. Patients who failed to respond to treatment after three months were crossed over to the opposite treatment, while responding patients were continued on the same treatment, in each case for another 3 months. A patient who failed the first treatment during the first 3 months and responded to the second treatment for the next 3 months was maintained on the second treatment for another 3 months. If response continued to be positive during this third 3-month period, the second treatment was counted as a successful treatment. To complete the study, a patient had to fail both treatments or have 2 successive periods (6 months) with a positive response.

A total of 62 patients completed the study from the 2 medical centers.

The authors of this paper, Drs. Parsons & Mullholland, had the following comments about their conclusions: "The findings in this study are similar to those from studies E-001 and E-002 reported above although improvement in this study used 50% or more improvement for inclusion in the improved group. It should be noted, however, that this study and studies E-001 and E-002 all used the intervals of 0, 25%, and 50% for measuring improvement, and in studies E-001 and E-002 no patients were included in the improved group whose improvement was estimated at 25%. Significantly more patients reported improvement in symptoms on Elmiron than on placebo, and voiding profile data revealed no significant differences between treatments. Adverse events were limited to skin rash in 1 patient during treatment with Elmiron. No mention is made about adverse events in the placebo group".

NOTE: This paper was also published as:

C.L. Parsons: "Sodium pentosanpolysulfate treatment of interstitial cystitis: an update". Urology, Suppl. Vol 29, April, 1987, p 14-16.

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2. M. Holm-Bentzen et al: "A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease". J. Urology, 137:503, 1987. (Ref. should be 138:503, 1987)

In this study sodium pentosanpolysulfate (Elmiron) was compared versus placebo in a prospective double-blind, clinically controlled, 7 center trial of 115 patients with "painful bladder disease" (sic).

Two protocols were used, Protocol A (43 patients) with clinically and pathologically anatomically verified interstitial cystitis (28 or more mast cells per mm²), and Protocol B (72 patients) with a "painful bladder and unspecified histological findings". The patients were randomized to receive either Elmiron (200 mg b.i.d.) or placebo capsules for 4 months. Patients were evaluated prior and after the trial with symptom grading, urodynamics, and cystoscopy with distension and deep bladder biopsies.

In the group of 43 patients with clinically and patho-anatomically verified interstitial cystitis, 39 patients (19 on Elmiron and 20 on placebo) completed the 4 months of treatment. In these patients, it was found that the reduction in pain was greater for the Elmiron treated group than for the placebo treated patients (no p values were given). In the Elmiron treated patients a statistically significant increase in bladder capacity was observed (under anesthesia), and "statistically significant improved cystoscopic appearance of the bladder".

Symptom scores measured in this study were not statistically significant different between groups. The authors state that: "if the number of patients in the study was augmented grossly, it might be possible to show an effect of sodium pentosanpolysulfate over placebo, but this effect would be of no clinical importance".

The following are reproductions of the comments by the sponsor: "The authors concluded that the results showed no difference between the pre-trial and post-trial values in the sodium pentosanpolysulfate and placebo groups in both protocols in regard to symptoms, urodynamic parameters, cystoscopic appearance and mast cell counts in patients with painful bladder disease".

"This study is confounded by the inclusion of a group of patients with "painful bladder disease" and suffers from the small number of patients with verified interstitial cystitis".

"Unfortunately, patients were not asked to give a self evaluation of the status of their disease and its symptoms at the end of the trial compared to the beginning of the trial".

The adverse reactions reported in this paper were: peripheral edema in 5 patients and skin rash in 1 who discontinued the therapy. Two patients complained of headache, nausea and dizziness and discontinued the treatment. There are no comments in this study of adverse reactions that may have been observed in the patients treated with the placebo.

The following is the table supplied by the investigators. It is submitted by the sponsor as a "Modified" (?) table from Holm-Bentzen et al. paper. Evaluation of symptoms in sodium pentosanpolysulfate trial. The data is confused, incomplete and without valuable conclusion.

Modified Table 4 from Holm-Bentzen et al paper
Evaluation of symptoms in sodium pentosanpolysulfate trial

	ELMIRON	Placebo	p
Total No. Patients	19	20	
with mean decrease of			
4 steps	6 (32%)	4 (20%)	>0.5
3 steps	8 (42%)	4 (20%)	>0.2
2 steps	9 (47%)	5 (25%)	>0.2
1 step	11 (58%)	9 (45%)	>0.5

UNCONTROLLED CLINICAL STUDIES:

The sponsor submits two studies under the section Uncontrolled Clinical Studies. The following is a brief review of these two investigations.

1. Fritjofsson et al.: "Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: a multicenter trial".
J. Urology, 138:508, 1987.

This study was performed at 17 centers in Finland and Sweden in 87 patients with symptoms of interstitial cystitis for more than 2 years.

The medication (400 mg daily in two doses) was discontinued after 6 months. Patients were evaluated every 4 weeks during the treatment and re-evaluated every 3 months for a follow-up.

There is a sponsor's comment at this time stating that "Not all observations were made in all patients at all centers".

It is reported that most of the patients responded favorably, some of them had a diminution of pain within 4 weeks from the start of treatment.

A relief of pain was reported in 60 patients, from this figure, total relief was observed in 21 (35%) and partial relief in 14 (23%).

The 24 hour frequency in urination decreased from 16.5 to 13.0.

The mean volume per void per 24 hrs was 66 c.c. before treatment in 84 patients, and 73 c.c. after treatment in 61 patients.

The nocturia decreased from 4.5 in 85 patients to 3.5 in 63 patients.

No other details submitted.

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2. C.L. Parsons, et al: "Successful treatment of interstitial cystitis with sodium pentosanpolysulfate".
J. Urology, 130:51, 1983.

This investigation included 24 patients suffering interstitial cystitis who had failed DMSO treatment and/or hydraulic bladder dilatation. They had nocturia 5 or more times per night or severe perineal or abdominal pain for a minimum of 3 years.

The medication was administered orally either 50 mg qid or 150 mg bid. Patients were evaluated after 4 weeks of therapy and then at month intervals for 6 to 24 months.

The authors reported that of the 24 patients, 20 had a decrease "of at least 80% in pain, nocturia, and urinary urgency, and 2 experienced a 50-80% reduction in symptoms".

In 3 patients Elmiron dosage was reduced by 50% after they had a significant relief in pain and nocturia. Upon recurrence of symptoms, these patients "responded to an increase in dose".

Two patients failed to respond to the medication.

No side effects were observed.

SPECIAL STUDY:

- Forestie F, Fischer AM, Daffos F, et al: "Absence of transplacental passage of pentosan polysulfate during mid-trimester in pregnancy". *Thromb. Haemo.* 56:247-249 (1986).

In this study 8 women scheduled for abortion between 8 and 23 weeks of pregnancy because of chromosomal abnormalities or hemoglobinopathies were given 50 mg of PPS intravenously.

Coagulation factors were studied before and after 30 minutes following this drug administration. Same coagulation studies were performed in blood drawn from the umbilical cord of the fetuses at 30 minutes after the administration of Eimiron (50 mg intravenously) to the mother.

The authors reported that: "These parameters in the fetal blood were compared to fetal blood from 16 control fetuses confirmed as normal at birth after having been tested for a prenatal diagnosis of toxoplasmosis at the 21st. week of gestation. In this study Activated Partial Thromboplastin Time was increased, Factor V was decreased, and Anti IIa generation was decreased in the mothers 30 minutes after injection of PPS, while there were no changes in any of the fetal blood parameters from the fetuses of these mothers compared to controls. These results as shown in Table 1 for the mothers and Table 2 for the fetuses, indicate that PPS does not cross the placental barrier." NOTE: Underlined by this M.O.

Table 1. Maternal coagulation factors before and 30 minutes after PPS

Parameter	Before PPS	After PPS
APPT (sec)	35 + 4	88 + 14
Factor V (%)	87 + 11	33 + 12
Factor II (%)	92 + 10	90 + 10
Factor X (%)	96 + 14	94 + 13
Anti Xa assay (IU/ml)	<0.05	<0.05
Anti IIa assay (IU/ml)	<0.05	0.1 + 0.03

PPS = pentosan polysulfate sodium

APPT = Activated Partial Thromboplastin Time

n = 8

Table 2. Fetal coagulation factors in control fetuses (n = 16) and in fetuses (n = 8) 30 minutes after maternal PPS

Parameter	Controls	PPS
APPT (sec)	93 + 9	91 + 6
Factor V (%)	42 + 8.5	48 + 6
Factor II (%)	14 + 4	13 + 5
Factor X (%)	22 + 3	21 + 4
Anti Xa assay (IU/ml)	N.D.	<0.05
Anti IIa assay (IU/ml)	N.D.	<0.05

PPS = pentosan polysulfate sodium

APPT = Activated Partial Thromboplastin Time

N.D. = Not Done

MEDICAL OFFICER'S COMMENTS

RESULTS OF STUDY:

- (a) Sponsor' evaluation.
- (b) Reviewer's evaluation.

SPONSOR'S EVALUATION:

The following are some of the results and conclusions the sponsor believes are supported by the study.

In the overview of the Clinical studies, the sponsor states that they are reporting in this submission the results observed by their investigators during two multicenter, double-blind, placebo-controlled using parallel, randomized groups of patients with the syndrome of interstitial cystitis. The trials were designed to evaluate the efficacy and safety of Elmiron (pentosan polysulfate sodium) for the amelioration of the symptoms of patients suffering interstitial cystitis.

The two protocols were very similar. They were designated as E-001 and E-002. They considered that according to their knowledge, these two studies were completed with the largest sample sizes of any previous study of a drug for use in interstitial cystitis.

The duration of the double blind period of the studies was chosen to be 3 months. The control was obtained by the administration of placebo during the time of the investigation. The sponsor clarifies that "The duration was selected because previous studies with Elmiron indicated that improvement was not immediate and it may take several weeks for patients to experience a reasonable degree of symptom relief, furthermore, the disease is known to wax and wane with patients reporting good days and bad days gradually changing in proportion toward more good days as treatment continues. Additional factors in the choice of study duration were the available information on the extent to which Elmiron is absorbed orally and excreted in the urine, and its mechanism of action. Since Elmiron is thought to act as a replacement for the protective glycosaminoglycan layer of the bladder which is believed to be injured or deficient in some manner, it may take some time for enough Elmiron to be deposited on the bladder wall to be effective. The 3 month period was therefore chosen as a reasonable time period for evaluating efficacy of Elmiron in this disease". Elmiron was provided for up to 2 years for study E-001 and for up to 1 year for study E-002. The sponsor clarifies that "Because the prolonged portion of the studies was designed as an open label one, the data obtained was not suitable for use as a factor of efficacy in the approval process. The data on safety would be useful to be recorded".

SPONSOR'S EVALUATION OF EFFICACY. Studies E-001 & E-002

The following are excerpts from the sponsor's conclusions:

There were three primary efficacy variables:

- I. The patients' self-evaluation of overall improvement as expressed on the Follow-up Questionnaire.
- II. Pain and urgency data from the Pain and Urgency Analog Scales.
- III. The Investigator's evaluation of overall improvement.

All of these evaluations were made after 3 months of double-blind therapy with Elmiron or Placebo.

I. First Primary Variable for Determination of efficacy:

a) Patients' self-evaluations--Overall Improvement.

At the end of the three-month double-blind period of the 2 studies, the patients completed the self evaluation form. Each patient evaluated their improvement over baseline in terms of pain, urgency, and overall disease on a 6 point scale from worse to excellent, and their improvement in sleep and sexual activity as yes or no.

"In both studies twice as many Elmiron patients as placebo patients evaluated themselves as having experienced more than 25% overall improvement in their disease and in both studies the difference between treatment groups was statistically significant. In all the evaluations, it should be noted that some evaluation forms were marked between the 25 and 50% levels of improvement and these are included in the more than 25% improvement group".

b) Patients' Self-Evaluations - Overall Improvement in Pain.

The results are similar in both studies, although the proportion of Elmiron patients reporting improvement in pain was slightly higher in study E-002. The sponsor elaborates that these results could be due to the higher number of patients treated under study E-002.

c) Patients' Self-Evaluations - Improvement in Urgency.

For urgency, the number of patients who experienced an improvement was higher in Study E-002 than in E-001 for both treatment groups. "The difference between treatment groups in favor of Elmiron approached significance in both studies using a 2-tail test of significance, but in study E-002 this difference was significant using a 1-tail test."

In relation to sex and sleep, these questions were only included in the self-evaluation form in study E-002. In this study there was no significant difference of improvement of sleep between patients treated with Elmiron and those treated with placebo: 41% in the Elmiron group and 39% in the placebo group. Regarding sex, the difference in improved sexual intercourse was 31% of 49 Elmiron patients versus 18% of 56 placebo patients. This approached significance ($p = 0.06$) using a 1-tail test. The sponsor considers that the reduced number of patients included in this analysis reflects the number of patients in this study who are not sexually active.

Using the sponsor's words: "For the patients' self-evaluation identified as the first of the three primary variables for establishing the efficacy of Elmiron compared to placebo, all the components of the self-evaluation, except for improved sleep, provided differences in favor of Elmiron that were statistically significant or approached significance in both studies using 1- or 2-tail tests".

II. Second Primary Variable for Determination of Efficacy.

a) Pain and Urgency Scale Data.

In both studies, each patient completed a pain and urgency scale at baseline (month 0), and at the end of months 1, 2, and 3. Patients rated their pain and urgency on a scale from 0 to 5 as None, Mild, Moderate, or Severe. They rated pain and urgency on separate scales according with these symptoms as for the past month. Patients were considered to have improved if they experienced a decrease of 1 point or more on the pain or urgency scales between months 0 and 3.

"In studies E-001 and E-002, when improvement in pain was defined as a reduction of 1 point or more on the pain scale, the differences in the number of patients experiencing improvement in pain in favor of Elmiron approached statistical significance in both studies at 3 months and at endpoint". The sponsor continues as follows: "Using the same 1-point reduction for urgency, the differences in favor of Elmiron were statistically significant in study E-002 at 3 month and at endpoint, but not in study E-001. The differences between the treatment groups in mean point change on these scales from baseline were not statistically significant in either study, although the changes from baseline in each treatment group were significantly different from zero." (underlined by this M.O.)

REVIEWER COMMENTS: It should be stated here that in Study E-001 Pain and Urgency were not considered by the sponsor as one of the Primary Efficacy Variables. In that study the variables used for determination of Elmiron efficacy were: 1) The patient's assessment of overall improvement.

2) The Investigator's assessment of overall improvement.

(See discussion of this decision from the sponsor in page 26 of this review)

III Third Primary Variable for Determination of Efficacy.

Investigator's Evaluation of Overall Improvement.

The investigators' overall evaluation was by using the 6-point scale from worse to excellent and based on discussion with the patient, as well as the data from the pain and urgency scales and voiding profiles.

The investigators' evaluation of overall improvement showed that in "both studies there were more than twice as many patients on Elmiron than on placebo who were rated as more than 25% improved overall. While the percentage of patients evaluated as improved was higher for both treatment groups in Study E-002 than in study E-001, the ratio of percent of patients improved between Elmiron and placebo was approximately the same in both studies; 26% versus 11% in study E-001 and 42% versus 18% in Study E-002 when all patients enrolled in the studies are used in the calculations. The higher level of efficacy in study E-002 may be related to the nature of the population used which was less refractory to conventional therapy and had a broader range of bladder capacity and voided volumes than the population in E-001."

Reviewer comments: This "Investigator's Evaluation of Overall Improvement" is rather ambiguous the conclusions are imprecise and this doesn't really say what the final evaluation of each study was.

SECONDARY EFFICACY VARIABLES:

Voided Profile Data.

The patients in both studies completed a voiding profile form. Each patient recorded at baseline (month 0) and after months 1, 2, and 3, for 3-days the number of night voids and the number and volume of each daytime void.

a) Nocturia - Average Change.

The difference between the treatment groups in nocturia were not statistically significant in either study for patients who completed 3 months or endpoint data. The change from baseline was significantly different from zero for Elmiron in E-001 and for placebo in both studies.

b) Frequency...

1) Average Change in Frequency.

The difference between treatment groups in average change in frequency from baseline was not statistically significant in either study for patients who completed 3 months or at endpoint. Some changes from baseline were significantly different from zero for both groups in Study E-002 but not in 001. (Underlined by this M.O).

2) Percent of patients with at least 3 less voids/day.

The sponsor states that the mean difference between treatment groups in relation to having a decrease from baseline of 3 or more voids per 24 hour day was not statistically significant for 3 months or at the endpoint in either study. There was a small difference in favor of placebo in both studies and "may relate to an increased intake of fluids in patients who felt better on Elmiron " (sic).

c) Urine volume.

1) Average change in volume per void from baseline.

An increase from baseline in mean volume per void was observed, although it was greater in Study E-002 than in Study E-001, and it was significantly different from zero in both treatment groups in Study E-002. In both studies, the trend was in favor of Elmiron but there were no significant differences between the treatment groups in either Study E-001 or E-002 in terms of the change from baseline in the mean volume per void.

2) Percent of patients with at least a 20 cc increase in average voided volume.

Using an increase of 20 cc or more per void as defined in the protocol to be a measure of improvement, the differences between the treatment groups, in favor of Elmiron were statistically significant in Study E-002 but not in study E-001 with both the endpoint and the three month data.

SPONSOR'S FINAL COMMENTS AND CONCLUSION.

DISCUSSION OF BENEFIT/RISK RELATIONSHIP AND PROPOSED POSTMARKETING STUDIES

The data included in this NDA submission, show that ELMIRON is effective for relief of the symptoms of interstitial cystitis in patients who have been shown to be essentially refractive to conventional therapy for this disease. The data from the Sponsor's double-blind placebo controlled trials are consistent with the data from studies in the published literature all of which are included in this NDA submission. In these studies significant relief of symptoms was reported by up to 50% of the patients enrolled and treated with 300 mg/day of ELMIRON for a 3 month double-blind period and continued on an open label basis for 1 or 2 years. In both of the Sponsor's double-blind trials, E-001 and E-002, ELMIRON was effective in more than twice as many patients as placebo.

In these same patients, ELMIRON was shown to be remarkably safe. In the Sponsor's double-blind trials, E-001 and E-002, the type and incidence of adverse events were not significantly different from the type and incidence of the adverse events reported in the placebo group. Adverse events were not evaluated for severity, but in only a few cases were they described as severe, and in no case as life threatening. In all the studies included in this NDA submission the incidence of adverse events fell in the range of 6 to 21% for ELMIRON and 9 to 13% for placebo. The most common adverse events using the Costart system were gastrointestinal and skin/appendages, consisting of nausea, diarrhea, and rash. There were no remarkable laboratory findings.

ELMIRON appears to be exceptionally safe in long-term therapy. In 142 patients from studies E-001 and E-002 continuing therapy for up to 1 or 2 years there were 4 adverse events reported, an incidence of 3% and one patient discontinued therapy because of an adverse event in this group.

The Sponsor's E-001, E-002, and Compassionate Use studies represent 897 patient years of ELMIRON therapy. During that time there have been a total of 135 patients reporting 234 adverse events without respect to relation to treatment. When only probably or possibly related adverse events are included, 103 patients reported 135 adverse events. This amounts to 0.15 adverse events per patient year of ELMIRON therapy or a patient report every 8.71 patient years.

On the basis of the data available and presented in this NDA submission the incidence of adverse events with ELMIRON therapy at a dose of 300 mg/day for the treatment of interstitial cystitis is low. At the same time, ELMIRON has been shown to have significant efficacy in about half the population treated, most of whom had been refractory to conventional therapy.

CONCLUSION

ELMIRON has been shown to be an effective and safe therapy in the treatment of interstitial cystitis.

MEDICAL OFFICER'S EVALUATION

This M.O. reviewed this Original NDA 20-183 submitted by the sponsor:
Baker Cummins
Pharmaceuticals
8800 Northwest 36th Street
Miami, Florida 33178

NAME OF DRUG:

Trade: Elmiron
Generic: Pentosan polysulfate sodium

DOSAGE FORM:

Capsules 100 mg.

ROUTE OF ADMINISTRATION:

Oral

PROPOSED INDICATIONS:

For the treatment of symptoms of Interstitial cystitis.

EVALUATION:

The sponsor submits a detailed results of the investigators' conclusions of these two studies considered as "pivotal":

- 1) "The Evaluation of Elmiron (Pentosan polysulfate sodium) in the Treatment of Interstitial Cystitis".
Protocol E-001
- 2) "An IND protocol for the Evaluation of Elmiron (Pentosan polysulfate sodium) in the Treatment of the Symptoms of Interstitial Cystitis".
Protocol E-002

Besides these two protocols there is attached also the results of a "compassionate" treatment IND entitled:

"A Treatment IND for the Compassionate Use of Elmiron (Pentosan polysulfate sodium) for Patients with Recurring Symptoms of Interstitial Cystitis".
Protocol: CE-001

Although without a complete and detailed review, the sponsor is relating some of their conclusions to the following two published papers under the Section: "Other double-blinded clinical studies"

C.L. Parsons & S.G. Mulholland, M.D. "Successful Therapy of Interstitial Cystitis with pentosanpolysulfate"
J. Urology, 138:513, 1987.

M. Holm-Bentzen et al: "A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the Treatment of Interstitial Cystitis and related painful bladder disease"
J. Urology, 137:503, 1987. (This reference should be 138:503, 1987).

The brief summaries of two uncontrolled studies are also submitted, although by reason of this specific type of study design they have not been taken in deep or serious consideration regarding their conclusion by the sponsor.

These two uncontrolled studies were:

Fritijofson et al, : "Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosan polysulfate: a multicenter trial"
J. Urology, 138:508, 1987.

C.L. Parsons, et al: "Successful treatment of interstitial cystitis with sodium pentosan polysulfate".
J. Urology, 130:51, 1983...

A "Special Study" was added to this submission:

Forestie F, Fischer AM, Daffos F, et al: "Absence of transplacental passage of pentosan polysulfate during mid-trimester in pregnancy".
Thromb. Haemo. 56:247-249 (1986).

the sponsor is basing their conclusions to the results of the "pivotal" studies submitted to this NDA, the primary evaluation by this M.O. will be regarding these aforementioned two studies, which are: E-001 and E-002.

For these two studies, the objectives, study design, methods of investigation, materials, selection of patients, sex, number, age, inclusion criteria, and exclusion criteria are considered adequate by this reviewer. The clinical investigators(*) and sites of investigation are also considered adequate.

(*) C. Lowell Parsons, M.D., who was one of the investigators in both studies E-001 and E-002, is the subject of the following comments by the sponsor, (page 5 396, vol. 10 of 20 vols):

"Prior to obtaining the rights to Elmiron, Dr. Parsons had a prior arrangement with sales of Elmiron. to receive a royalty on the this contractual arrangement". That statement from the sponsor was sent to was obligated to continue with the Office of Compliance, Division of Scientific Investigations for review and advice.

This is a summary of these studies and patient characteristics

		E-001	E-002
No. of Centers		5	7
No. of patients enrolled	Elmiron	54	74
	Placebo	56	74
Completed 3 months	Elmiron	51	65
	Placebo	47	65
Dropped out (*)	Elmiron	3	9
	Placebo	9	9
Mean disease duration (yrs)	Elmiron	7.4	6.6
	Placebo	5.8	6.6

(*) The reason/s for these dropouts were already discussed; although a very few of patients dropped out because some adverse reaction/s these were not severe or with important clinical significance. The majority of patients that did not end the studies were dropped because they failed to return to complete treatment or failed to return for evaluation at first, second or third months of treatment.

SAFETY EVALUATION:

Based in the reports submitted by the sponsor regarding studies E-001 and E-002, Elmiron appears to be without serious safety problems. The type and incidence of adverse events were not significantly different from those events observed in patients in the placebo group. There were no events recorded as serious, and in no case as life threatening. The most common adverse events were gastrointestinal (nausea, diarrhea), some skin reactions (rash, pruritus), and nervous system (headache and dizziness).

In relation to the "Compassionate Use of Elmiron", as this M.O. stated in the review of that specific IND, this Office did not receive enough information either from the investigators or the sponsor. No progress Reports were made available to us during the periods of administration of this drug. For that reason it is very difficult to have a complete and reliable evaluation of the events and details of those patients. The sponsor states there have been 1274 patients included and treated under this Compassionate Use protocol, and that "221 patients reported 366 adverse events, irrespective of drug relationship. If only possible or probable related events are included, 142 patients reported 221 events".

LABORATORY TESTS:

The laboratory data obtained during the studies did not show severe or important deviations from normal in the parameters from blood or urine tests. In spite of this drug being related to heparin no consistent effects were observed on the coagulation studies. Apparently the anticoagulant effect of Elmiron has been estimated to be one fifteenth that of heparin.

In E-001 at three months, mean PTT was significantly higher ($p=0.07$) in the placebo group (29.75 sec.) than with Elmiron (28.39 sec.) while E-002 at three months, PTT was significantly higher ($p=0.084$) with Elmiron (29.4 sec.) than with placebo (27.6 sec.).

[Reviewer's comment: These changes suggest that the anticoagulant effect of Elmiron is inconsistent and probably of no clinical significance.]

Some changes were observed in serum calcium which was found to be elevated at three months of therapy in the Elmiron group, 9.57 mg% vs. 9.36 mg% in the placebo group.

It is also interesting to note that in study E-001 but not in E-002 there were some changes in other laboratory parameters, e.g. monocytes, PT, and potassium. In each of them was a mean increase from baseline which was significantly different from zero, but not different from placebo and not outside the normal range.

The following is quoted from the second paragraph, page 5 351 vol 9 of 20 vols. "The laboratory data from the patients in the Sponsor's Compassionate Use study were reviewed as received every 3 months and values outside the normal range were noted. Although no detailed analysis has been done, no pattern has been detected in any of the parameters that would suggest that a problem with Elmiron exists". This paragraph is reproduced here because, as this reviewer stated, we have not received enough information from the investigators involved in the Compassionate Use study*

LONG TERM ADVERSE EFFECTS:

The experience obtained from the long term administration of Elmiron has shown the incidence of adverse effects to be low. The sponsor is including in these results the investigators' reports which are based in studies E-001, E-002, the Compassionate Use study and the Parsons' & Mulholland's paper published in 1987.

In study E-001 after the termination of the 3 month double-blind treatment, patients were given the opportunity to continue with Elmiron therapy on an open label basis for up to 2 years; the patients in study E-002 were given the same opportunity to continue for up to 1 year. Regarding the Compassionate Use study the patients could continue on controlled therapy "for as long as they felt they were getting satisfactory relief of their symptoms". It is reported that in this Compassionate Use study there have been 44 patients on Elmiron therapy with "continuing efficacy for 2 years up to more than 5 years as of December 31, 1989".

(*) NOTE: In this reviewed submission there is no information of a follow-up of these patients with changes in their laboratory parameters after administration of Elmiron. It is the opinion of this reviewer that those deviations should be reevaluated in order to verify if and when they returned to baseline values. The same information must be obtained during the long term administration of Elmiron and after discontinuation of therapy.

The following is a table provided by the sponsor (table 26) under the title: "Number of patients on Elmiron therapy for more than 24 months".

Months on Elmiron	No of patients
6	
More than 6 & less than 9	80
More than 9 & less than 12	31
More than 12 & less than 18	31
More than 18 & less than 24	46
More than 24	31
	22
Total	241

The sponsor elaborates some explanations related to the long-term use of Elmiron in patients treated under the Compassionate Use study. As per their figures, already discussed by this M.O. in another part of this review, they reported that 1274 patients have been on therapy with Elmiron "with continuing efficacy" for 2 years to more than 5 years as of March 15, 1991.

The following is the table (table 2) related to the patients treated under the Compassionate Use study: "Number of patients on Elmiron therapy for periods of 6 months to more than 24 months":

Months on Elmiron	Number of patients
6 - 12	
12 - 24	211
24 - 36	143
More than 36	94
	49
Total	497

DRUG-DRUG INTERACTIONS:

Considering that Elmiron is a heparin like drug, when these two drugs were given together the possibility of additive anticoagulant effect was taken in consideration, but no severe change in coagulation was observed; it has been estimated that the anticoagulant effect of Elmiron is one fifteenth that of heparin.

Finally, it is stated that Elmiron has been administered concomitantly with other drugs used as adjunctive therapy for interstitial cystitis, such as DMSO, corticosteroids, etc. as well as with drugs for other conditions such as diabetes, heart disease and pain, without reported interactions with any of these concomitant drugs.

TOXICITY: On the basis of the animal toxicity data submitted, this drug meets the definition of practically non-toxic. It appears to have no teratogenic or mutagenic activity in either the micronucleus assay or the Ames test.

EFFICACY EVALUATION:

The sponsor submits several different tables related to the symptoms evaluated by the patient and by the investigator. There are problems observed during the review of the results of this investigation which make a complete and accurate conclusion somewhat difficult to obtain..

First of all, no completed Case Report Forms are included. We received (and not in-toto) some of the Case Report Forms of patients who dropped for one reason or another from the study (Pages 5 580 through 5 715, vol. 10 of 20 vols.).

REVIEWER EFFICACY EVALUATION (Study E-001):

In this study the Primary Measurements used by the sponsor to determine Effectiveness of Elmiron were:

- I.- Patient assessment of overall improvement as compared to pretreatment
- II.- The Investigator's assessment of overall improvement.

The sponsor states that the other individual symptoms of interstitial cystitis i.e. frequency, urgency, pain, nocturia and average voided volume although recorded by the patient, were not considered as elements of primary efficacy, but "were only considered as supportive data".

At this time it is interesting to notice that in Study E-002 besides the overall evaluation by the patient and by the physician, the sponsor is adding Pain and Urgency Scale Data as another element of the Primary Efficacy Evaluation.

Final number of patients treated Study E-001:
 Patients on Elmiron that completed the study.....51
 Patients on placebo that completed the study.....47

OVERALL EVALUATION SUMMARY.- Severity of disease = Moderate.

Response	Outcome	Elmiron	Placebo	p-value
Overall Patient Evaluation	Better	6 (25%)	4 (17%)	0.72
	Not Better	17 (74%)	19 (83%)	
Overall Investigator Evaluation	Better	6 (26%)	4 (17%)	0.72
	Not Better	17 (74%)	19 (83%)	

OVERALL EVALUATION SUMMARY Severity of Disease = Severe.

Response	Outcome	Elmiron	Placebo	p-value
Overall patient Evaluation	Better	9 (29%)	3 (9%)	0.05
	Not Better	22 (71%)	30 (91%)	
Overall Investigator Evaluation	Better	8 (26%)	2 (6%)	0.04
	Not Better	23 (74%)	31 (94%)	

As can be observed in these two tables considered as the Primary Efficacy Variables in this Study, the number of patients treated with Elmiron who achieved improvement is very small. Independently of any statistical significance obtained, from practical clinical standpoint the results regarding efficacy are not as optimistic as the sponsor states.

These tables are reviewed in pages 35 and 36 of this M.O.'s review and they are summarized in pages 5 794 and 5 795 vol. 10 of 20 vols. of this submission.

The other variables of efficacy were evaluated and described in different tables as follows:

PAIN SUMMARY:

Table 4.- Rate of pain at month 0 and at the end of the third month of treatment.

Table 5.- Change of pain from end of month 1 to end point.

Table 6.- Improvement in pain from baseline to the end of the double blind treatment.

These tables are presented in page 28 of this review and pages 5-765 through 5-769 in volume 10 of 20 vols. of this submission.

URGENCY SUMMARY:

Table 7.- Rate of urgency (0=none to 5=severe) at each month of the double blind treatment period (months 0 to 3) and at the end point

Table 8.- Rating of urgency (0=none to 5=severe) from month 0 to each month and at the end point.

Table 9.- Summary of patient improvement in urgency in patients treated with Elmiron compared to patients treated with placebo, from baseline to the end of third month (end of the double-blind treatment).

These tables are presented in pages 28 and 29 of this review and pages 5-770 through 5-774 in volume 10 of 20 vols. of this submission.

REVIEWER'S COMMENTS:

Besides the fact that in tables 4, 5, 6, 7, 8, and 9 no statistically significant differences between groups were found, we have to conclude that from clinical and urological standpoints the improvement of these symptoms cannot be qualified as significant in support of the efficacy of this drug.

VOIDING PROFILE:

- Table 10.- Summary of number of voids per day (24 hours) from baseline to each of the three months of treatment and at end point.
- Table 11.- Summarizes the change of the number of voids per day (24 hours) from baseline (month 0) to each of the three months of treatment and at end point.
- Table 12.- Improvement of number of voids per day (24 hours) from month 1 to each of the three months of treatment and at end point. A patient is better if there is at least a reduction of 3 voids per day.
- Table 13.- Summary of the number of voids per night (from 12 p.m. to 7 a.m.) at each month (0 through 3) and at end point.
- Table 14.- Summarizes the change of the number of voids per night from baseline (month 0) through each month and at the end of the third month of treatment (end point).
- Table 15.- Summary of the volume per void in c.c. from month 0 through 3 and at endpoint.
- Table 16.- Summary of the change of volume per void (c.c.) from baseline to each of the three months of blind treatment and end point.
- Table 17.- Summary of improvement in volume per void at each month and at end point. Patient is better if there is at least a 20 c.c. increase in volume of urine per void.
- Table 18.- Summary of total daytime volume voided (c.c.) from month 0 through the end point.
- Table 19.- Summarizes the change of the total daytime volume voided (c.c.) from baseline to the end of the third month of treatment (end point).

A description of these tables are in pages 29, 30 and 31 of this M.O.'s review, and in pages 5-775 through 5-791 in vol 10 of 20 vols. of this submission.

REVIEWER'S COMMENTS:

In reviewing these tables some problems were observed: In some of them there was inconsistency between the figures. For example: in table 11, in relation to the change of number of voids in patients on placebo, the difference between baseline and the end of the third month should be 0.9 instead of 1 (as it is stated).- In table 14 the change of number of voids per night from baseline to end point should be 0.7 in patients in Elmiron and 0.4 in patients on placebo., instead of 0.8 and 0.5 respectively.

In table 15 the volume per void in c.c. comparing the volume at month 0 versus the volume at the end of the third month was as follows:

GROUP	AT MONTH 0	END OF THIRD MONTH	CHANGE
Elmiron	89.2 c.c.	96.0 c.c.	6.8 c.c.
Placebo	91.1 c.c.	100.6 c.c.	9.5 c.c.

In table 16 the change of volume per void was described as:

Elmiron	9.5 c.c.	9.8 c.c.
Placebo	5.3 c.c.	7.6 c.c.

The inconsistency and inaccuracy of those figures is apparent. In the analysis of tables 14, 15, 16, and 17 no statistically significant treatment group differences were found; and more important than statistics, the symptom improvements after Elmiron are practically insignificant.

The table 19, is entitled: "Summary of total daytime volume voided (c.c.). Change from baseline". This table, described in this M.O.'s review in page 31 and pages 5 748 and 5 749 and table 20 (page 5 759, vol 10 of 20 vols of this submission) is difficult to interpret as per data submitted.

The figures that are presented by the sponsor can be summarized as follows:

GROUP	END OF FIRST MONTH	END OF THIRD MONTH.
Elmiron (50 pts)	114.6 c.c.	60.1 (50 pts)
Placebo (50 pts)	-14.5 c.c.	-6.5 (45 pts)

Although the following paragraph written by the sponsor regarding this table was reproduced in page 31 of this review, it may be useful to be repeated here. "An examination of the means for each site (Table 19) shows that the result from site 2 was very different from that of the other sites. For example, at end point for site 2 the mean change for the placebo treatment group was 439.6 c.c. compared to -213.1 cc for the Elmiron group. For the remaining sites the treatment group means were either similar or showed the Elmiron group to have an increase greater than that of the placebo group. Overall sites the Elmiron group had a mean increase in daytime volume of 60.1 cc while the placebo group had a mean decrease of 20.1 cc".

EFFICACY EVALUATION

Study E-002:

For this study the Primary Measurements used by the sponsor to determine Effectiveness of Elmiron were:

- I.- Patient's evaluation of Overall improvement.
- II.- Patient's evaluation of Pain and Urgency (as per Pain and Urgency Scales).
- III.- Investigator's evaluation of overall improvement.

Seven investigators in seven different sites were involved in this study.

<u>Final number of patients treated</u>		Study E-002
Patients on Elmiron group	65	
Patients on placebo group	65	

I.-PATIENT OVERALL EVALUATION OF IMPROVEMENT. (Number of patients).

Patients evaluated themselves at the end of the 3 month treatment period; if an improvement of more than 25% was found in their personal assessment the patient was classified as better, otherwise not better. It is stated that patients who left the study early were declared not better.

Patient Overall Evaluation of Improvement. (Number of patients)								
Treatment	Site							Total
	1	2	3	4	5	6	7	
ELMIRON								
Better	10	1	2	5	1	1	4	24 (32%)
Not better	5	15	3	11	3	5	8	50 (68%)
Placebo								
Better	2	1	0	5	2	2	0	12 (16%)
Not better	12	16	4	11	2	6	11	62 (84%)

REVIEWER'S COMMENTS:

It is observed that by this table 24 patients (32%) improved with the administration of Elmiron, vs. 50 (68%) that did not get better. It should be noticed that there is a disparity and inconsistency of the results obtained in the seven sites when compared one to each other. This disparity is more noticeable in site 2.

II.- PATIENT'S EVALUATION OF PAIN AND URGENCY (as per scales).

A.- Pain Evaluation

Assessment of pain was based on change in rating scale from baseline to endpoint. If an improvement of at least one point on the analog scale was found the patient was classified as better, otherwise not better.

At this time this reviewer would like to comment about the fact that in some of the tables submitted there was an statement by which "Patients whose rate of pain at baseline (visit 0) was zero are excluded from this analysis". Although the sponsor clarifies that exclusion in relation to the endpoint of analysis, it is the opinion of this reviewer that if pain was one of the criteria for entrance in this investigation, patients free of pain should never have been admitted into this study. The admission in these studies of patients free of pain produces some confusion in relation to the end results; it is impossible to evaluate for other parameters patients who by criteria of entrance should not be included in this investigation.

Pain-based on Change in Rating Scale

GROUP	Outcome	Site							Combined
		1	2	3	4	5	6	7	
Elmiron	Better	9	9	4	9	2	5	5	43 (63%)
	Not Better	5	5	1	5	2	1	6	25 (37%)
Placebo	Better	5	9	0	11	2	3	4	34 (52%)
	Not Better	7	6	3	4	1	5	6	32 (48%)

Pain-Based on Patient's Final Examination. (Overall Evaluation)

Elmiron	Better	11	1	2	5	2	2	5	28 (38%)
	Not Better	4	15	3	11	2	4	7	46 (62%)
Placebo	Better	2	1	0	6	2	2	0	13 (18%)
	Not Better	11	16	4	10	1	6	11	59 (82%)

REVIEWER COMMENT: The first of these two tables shows a percent favoring Elmiron to placebo, but in the final examination the results are inverted. The inclination toward the Site 2 is observed again.

B.- URGENCY EVALUATION:

Patient final evaluation of reduction in urgency (number of patients)
 Percent of patients evaluating their improvement in urgency as more than 25%
 (at the third month self evaluation)

Treatment	Site							Total
	1	2	3	4	5	6	7	
Elmiron								
Better	9	1	2	5	1	1	3	22 (30%)
Not Better	6	15	3	11	3	5	9	52 (70%)
Placebo								
Better	2	2	0	5	1	2	1	13 (18%)
Not Better	12	15	4	11	3	6	10	61 (82%)

The results as per the above table shows that patients who were treated with Elmiron improved in their urgency 30% vs. 70% of the patients that did not improve.

This table shows again a distinctive difference of results obtained in site 2 when compared with the other 6 sites.

Urgency-Based on Change in Rating Scale.

Elmiron								
Better	12	6	4	3	2	4	6	42 (62%)
Not Better	2	8	1	6	2	2	5	26 (38%)
Placebo								
Better	4	7	0	8	3	3	4	29 (43%)
Not Better	9	8	3	7	1	5	6	39 (57%)

The results as per the above table shows a definite reverse of the figures obtained when compared to the previous one. This shows again the inconsistency of the end results regarding efficacy obtained.

III.- INVESTIGATOR'S EVALUATION OF OVERALL IMPROVEMENT (Number of patients)
 If an improvement of more than 25% is found the patient is classified as better, otherwise not better. Patients who left the study early were declared not better.

Treatment	Site							Total
	1	2	3	4	5	6	7	
Elmiron								
Better	11	1	1	5	1	1	7	27 (36%)
Not Better	4	15	4	11	3	5	5	47 (64%)
Placebo								
Better	2	1	0	4	2	2	0	11 (15%)
Not Better	12	16	4	12	2	6	11	63 (85%)

REVIEWER'S FINAL COMMENTS.AND RECOMMENDATIONS:

The final comments may be summarized into four different aspects of this submission:

- 1.- The accuracy of the data submitted.
- 2.- The safety of the administration of this drug.
- 3.- The efficacy of Elmiron in the treatment of symptoms of Interstitial Cystitis.
- 4.- Review of the proposed text of the Package Insert.

1. In reviewing the tables submitted, very often a discrepancy is found between the final number of patients treated in each of the two "pivotal" studies E-001 and E-002. The sponsor stated that the final number of patients that could be evaluated in Study E-001 was 98, divided into 51 patients in the Elmiron group and 47 in the placebo group. The final number of patients that could be evaluated in Study E-002 were 130, divided into 65 in Elmiron group and 65 in the placebo group. Without analyzing here each of the tables submitted related to the final number of patients treated, it should be pointed out that very often discrepancies were observed between the number of patients analyzed and the total number of patients that were supposed to enter in each study.

Another problem which may be considered a protocol violation was related to the following comments stated by the sponsor in some of the tables: "Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis". This fact was already discussed by this M.O. (page 89 of this review). In spite of some explanation given by the sponsor by which those patients were excluded from analysis, it is clear that patients free of pain should never have been admitted into these studies taking in consideration that one of the criteria for admission in these investigations as a diagnosis of interstitial cystitis was the presence of pain.

It should be commented again that the sponsor failed to submit to this NDA the completed Case Report Forms of patients treated under both Studies as well as no tabulation of individual responses to treatment.

2. Regarding safety, this was discussed in pages 82-83 and 84 of this review. Elmiron appears to be without serious safety problems. The incidence of adverse events were without important clinical significance and in no case described as life threatening.
- 3.- Efficacy.- Although the studies demonstrated that Elmiron has beneficial effect in some of the symptoms of interstitial cystitis, this M.O. cannot state that these investigations demonstrated that those problems were solved in the majority of the cases nor that the improvements could be qualified as impressive or completely conclusive. There were patients that improved at a clinically demonstrable level, but the improvement of the majority of patients were none or minor. The limited data available suggest that patients having more severe symptoms at the initiation of therapy may show better response than those with lesser symptoms.

At this time this M.O. would like to quote some of the final comments from James Gebert, Ph.D, Mathematical Statistician, HFD-713m who reviewed this submitted NDA: "The evidence of efficacy of Elmiron for the treatment of interstitial cystitis is very weak. Of the four primary efficacy variables (patient overall, investigator overall, pain-based on change in rating scale and urgency-based on changing in rating scale) only patient and investigator overall were significant ($P = .04$) in Study E-001, (These measures would be expected to be highly correlated). Three of the four variables (patient and investigator overall evaluation and urgency - based on change in rating scale) were significant in Study E-002. In each study there is one influential center (Dr. Hanno in Study E-001 and Dr. Parsons in Study E-002) that was the main contributor to the significant results seen."

In the last paragraph Dr. Gebert stated: "If the influential center is excluded in study E-002, none of the primary efficacy variables show statistical significance". "If the influential center is excluded from study E-001, three of the four primary efficacy variables are not significant".

REVIEW OF THE SUBMITTED PROPOSED TEXT OF THE PACKAGE INSERT.

DESCRIPTION

Satisfactory.

CLINICAL PHARMACOLOGY

Satisfactory.

INDICATIONS AND USAGE

Not satisfactory.

This section should be revised as follows:

CONTRAINDICATIONS:

Satisfactory.

WARNINGS

Satisfactory.

PRECAUTIONS:

Not satisfactory.

The first paragraph of this section should be reworded as follows:

ADVERSE REACTIONS:

Satisfactory.

OVERDOSAGE

Satisfactory.

DOSAGE AND ADMINISTRATION

Satisfactory.

HOW SUPPLIED

Satisfactory.

CONCLUSION:

Considering the fact that at present time there is no other drug with more evidence of efficacy than Elmiron to treat the symptoms of Interstitial Cystitis, this M.O. recommends that this NDA be approvable. However, the wording in Indications and Usage and Precautions sections of the submitted package insert should be revised.

These revisions in the package insert should be performed in order to reflect that Elmiron may ultimately be shown to be a useful alternative in the urologist's or the medical practitioner's armamentarium for palliative treatment of these unfortunate patients, but on the basis of presently available data it should be clearly specified that this medication cannot be considered without doubt as an infallible drug to be prescribed for the treatment of the complex symptoms of Interstitial Cystitis.

Chalon Rodriguez, M.D.
Chalon Rodriguez, M.D.

c.c.: Original NDA 20-193
HFD-160/Division File
HFD-160/Chalon Rodriguez, M.D. (reviewer)
HFD-160/Stewart (chemist)
HFD-160/Wilson (pharmacologist)
HFD-160/Rhee (C.S.O.)
R/D Initiated by J.C. Kenealy, M.D.
F/T by Chalon Rodriguez, M.D.
Wang 3145F

See Division Director's Review
and Comments dated 2/18/52
[Signature] mo

SAFETY UPDATE REVIEW

See Deputy Director's Memo dated September 23, 1996.

Clin. Pharm.
and Bio

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-193

REVIEWER: David J. Lee, Ph.D.

DRUG: Elmiron® Capsules, 100 mg, 300 mg/day

SUBMISSION DATE: 4/10/96,
8/12/96

APPLICANT: Baker Norton Pharmaceuticals, Inc.

RECEIVED DATE: 4/30/96

TYPE OF SUBMISSION: Amendment to the Approvable Letter

REVIEW DATE: 9/16/96

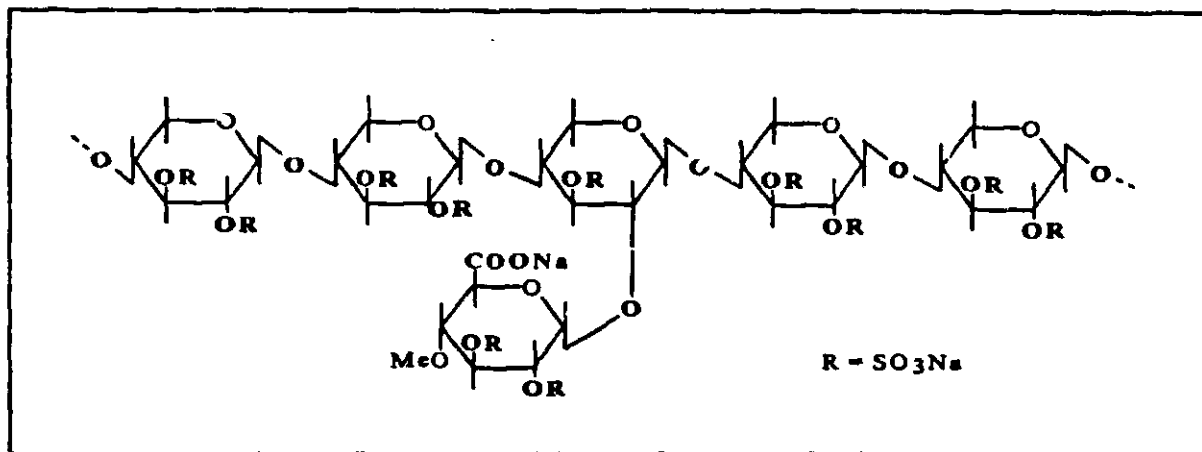
SYNOPSIS

Baker Norton Pharmaceuticals, Inc. has submitted NDA 20-193 Amendment for the approval of Elmiron® Capsules, 100 mg. The active ingredient in Elmiron is pentosan polysulfate (PPS). Elmiron is indicated for the treatment of interstitial cystitis (IC). It is presumed that PPS acts by adhering to the exposed (denuded) mucosal layer of the bladder epithelium and coats the denuded areas. PPS binds water strongly thereby restoring the normal barrier between the epithelium of the bladder and the urine, which is thought to be irritating to the denuded areas.

In the current amendment, the applicant submitted an amendment to the Division's Approvable Letter dated March 1, 1996. The applicant resubmitted the pharmacokinetic study reports (3 bio-studies) conducted by Greenslade, Fellstrom and Kummer. It also contains literature references relating to PPS and IC.

In addition, the applicant submitted an *Information Amendment* on August 13, 1996 (Stamped date) to address the questions posed by this reviewer regarding the PPS formulation used in the clinical pharmacokinetic studies (3 bio-studies).

PPS Structure



BACKGROUND

The original NDA 20-193/1-C was submitted on June 11, 1991. The Division of Biopharmaceutics (now the Office of Clinical Pharmacology and Biopharmaceutics) concluded that the 3 pharmacokinetic

studies submitted has not adequately described the bioavailability/pharmacokinetics of PPS in order to comply with 21 CFR 312.21, and is not adequate to support its approval as well as support its labeling (Dr. Daniel Gordin, Review Stamped Date: 2/25/1992). On January 27, 1993 (Stamped Date), the Division of Medical Imaging and Radiopharmaceutical Products issued a first "Not Approval" letter to the applicant. According to the HFD-160's division drug file, it is not clear if Dr. Gordin's comments were forwarded to the applicant.

On July 7 and 20, 1993, the applicant resubmitted limited dissolution data available for different Elmiron capsule formulations used in the two efficacy clinical studies and submitted a new protocol (Urinary Concentration-Controlled Trial of Elmiron). Dr. Gordin indicated that the applicant did not use the to-be-marketed capsule formulation in 3 bio-studies. In addition, the sponsor's resubmitted dissolution information was found to be inadequate. Dr. Gordin stressed that in the urinary concentration-controlled trial, the patients should be administered with the to-be-marketed formulation in order to avoid a bioequivalence issue, because of this product's very low systemic bioavailability (review attached: Stamped Date 10/13/1993).

On October 28, 1994 (Stamped Date), the Division of Medical Imaging and Radiopharmaceutical Products issued a second "Not Approval" letter to the applicant based on the inadequate data. In this letter, the Biopharmaceutics comments were forwarded to the applicant.

On August 31, 1995, the applicant submitted an additional safety and efficacy data. The amendment was reviewed by this reviewer and recommended "Not Approval" from a Biopharmaceutical perspective based on the fact that the applicant did not submit any new additional pharmacokinetic information in the amendment (January 29, 1996, Review Date). This reviewer concurred with the previous decision that bio-data (3 bio-studies) submitted has not adequately described the bioavailability/pharmacokinetics of PPS. In addition, this reviewer recommended that if this NDA is approved, the applicant should commit to perform Phase IV human pharmacokinetic studies with the to-be-marketed PPS formulation to define PPS pharmacokinetic and metabolic profile.

RECOMMENDATION

The current amendment submitted by the applicant on 4/10/96 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). Based on the information, this reviewer considered that the amendment still does not adequately address the deficiencies previously indicated for this drug product. This application is not acceptable from a Clinical Pharmacology/Biopharmaceutical perspective due to the following reasons:

1. Formal assay validation data are not available, although the applicant attempted to locate these data;
2. The original pharmacokinetic review indicated that the 3 bio-studies did not employ a sufficient number of study subjects to draw conclusions of the kinetics of PPS;
3. The 3 bio-studies did not characterize the kinetics of PPS using the proposed 100 mg dose or t.i.d. dosing regimen administered 1 hr before or 2 hrs after a meal;
4. Two different capsule formulations which vary with microcrystalline cellulose content (80 mg vs. 123 mg) were used in the 2 pivotal clinical studies E-001 and E-002. The applicant indicated that the to-be-marketed formulation will use 123 mg cellulose formulation; however, bioequivalence/availability data comparing the 2 formulations was not submitted. According

to the original pharmacokinetics review, the dissolution results submitted by the applicant comparing the 2 formulations is not adequate to make a comparison since only 2 capsules were used from each lot. In addition, these lots used in the pivotal clinical studies have expired at the time of review;

5. The applicant did not submit a food effect study. In the 3 bio-studies, PPS was administered after fasting which continued for 4 hrs post administration. The bioavailability of PPS may change under nonfasting conditions.

It should be noted that the applicant is planning to conduct radiolabeled studies of PPS to further define the metabolic profile of PPS in healthy volunteers as well as in patients with hepatic impairment.

Drug Labeling comments: This reviewer recommends that the pharmacokinetic information in the labeling should be updated with the information obtained from the Phase IV pharmacokinetic studies, which will include pharmacokinetic information regarding subjects with hepatic impairment and patients taking anticoagulants. The package insert should indicate that the PPS pharmacokinetic parameters presented are preliminary information obtained with the clinical PPS formulation and will be revised once the Phase IV studies are conducted with the to-be-marketed formulation.

COMMENTS TO BE CONVEYED TO THE APPLICANT

1. **Phase IV Commitments by the applicant**

The applicant indicated that they will conduct radiolabeled studies of PPS to further define the metabolic profile of PPS in healthy volunteers as well as in patients with hepatic impairment. The applicant should submit protocols to the agency prior to conducting the studies. The following questions should be considered:

2. **Labeling Comments**

In addition to labeling edits conducted by HFD-160 Division Director and Deputy Division Director, the following comments are made by this reviewer :

ADDITIONAL REVIEWER'S COMMENTS (NOT TO BE CONVEYED TO THE APPLICANT)

The following questions, which were raised from the previous submissions and amendments by this reviewer, needed clarification although the applicant responded in the submission dated August 12, 1996 (questions #2 and 3; See attached).

Reviewer's Comment: It is still unclear to the Office of Clinical Pharmacology and Biopharmaceutics what moieties were being measured during the pharmacokinetic studies. Therefore, all data regarding pharmacokinetic parameters are still in question.

Reviewer's Comment This information clarified the 'to-be-marketed' formulation in terms of molecular formula, $[C_5H_8O_4(SO_3Na)_2]_n$, n, and its average molecular weight (MW). The applicant's response appears to be adequate; however, the reviewing chemist should be consulted to verify the applicant's statement, in particular, the inappropriately calculated value of 17.

Reviewer's Comment It is most likely that the 3 bio-studies were conducted with the drug substance with the same molecular-weight distribution as the to-be-marketed formulation, which has n = 11 xylose units. According to the Chemistry Review, the reported chain length was n = 11 on May, 1993 (which concurs with the statement in question #1):

Chemistry Review Date	Approximate Chain length, n	average MW
11-15-91	17	5700
5-28-93	11	3676
9-8-93	11	3676
4-13-94	11	3676
12-05-95	11	3676

The chain length may play a major role in pharmacokinetics (the distribution and elimination characteristics may change with different chain lengths), and perhaps efficacy (whether the intact or metabolized PPS is adhered to the denuded areas) of this drug. The clinical pharmacology describes the possible mode of PPS action as follows:

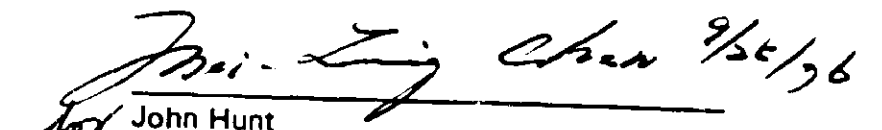
"It has been suggested that in patients with IC, the bladder has areas which are denuded of the glycosaminoglycan layers. Therefore, a proposed mechanism of action of PPS in this disease is that it (i.e., intact PPS molecule or not-metabolized PPS) binds to the transitional epithelium of the bladder and coats the denuded areas. PPS binds water strongly thereby restoring the normal barrier between the epithelium of the bladder and the urine which is thought to be irritating to the denuded areas."

However, although the applicant did indicate that the 3 bio-studies were conducted with the *drug substance* with the same molecular-weight distribution as the to-be-marketed formulation, it is not confirmed that the formulation, which includes other excipients such as microcrystalline cellulose, used in the 3 bio-studies was the same formulation as the to-be-marketed formulation.

 9/25/96

David J. Lee, Ph.D.
Pharmacokineticist
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

 9/25/96
for John Hunt
Deputy Director
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: HFD-160 NDA 20-193
HFD-160 DIV FILE
HFD-160 /CSO/SCUSACK(1X)
HFD-870 /OCPB/JHUNT (1x)
HFD-160 /OCPB/DLEE (1x);
HFD-860 /OCPB/HMALINOWSKI (1X)
HFD-870 /OCPB/MLCHEN (1X)
HFD-880 /OCPB/NFLEISCHER (1X)
HFD-850 /OCPB/LLESKO (1X)
HFD-850 /OCPB/CBOTT/CHRON., DRUG, REVIEWER (3X)
HFD-340 /VISWANATHAN (1X)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-193	REVIEWER: David J. Lee, Ph.D.
DRUG: Elmiron® Capsules, 100 mg	SUBMISSION DATE: 8/31/95
APPLICANT: Baker Norton Pharmaceuticals, Inc.	RECEIVED DATE: 1/19/96
TYPE OF SUBMISSION: Amendment	REVIEW DATE: 1/29/96

SYNOPSIS

Baker Norton Pharmaceuticals, Inc. has submitted NDA 20-193 Amendment for the approval of Elmiron® Capsules, 100 mg. The active ingredient in Elmiron is pentosan polysulfate (PPS) which is indicated for the treatment of interstitial cystitis (IC). It is presumed that PPS acts by adhering to the exposed mucosal layer of the bladder epithelium.

In the current amendment, the applicant submitted no additional pharmacokinetic information. However, the reviewing medical officer, Dr. Lori Paserchia, requested a review of the pharmacokinetic information listed in Elmiron's Investigator's Brochure.

BACKGROUND

The original NDA 20-193/1-C was submitted on June 11, 1991. Based on the review of the submitted pharmacokinetic information (3 bio-studies), the Division of Biopharmaceutics (Dr. Daniel Gordin, Review Stamp Date: 2/25/1992) concluded that the bio-data submitted has not adequately described the bioavailability/pharmacokinetics of Pentosan Polysulfate in order to comply with 21 CFR 312.21 and is not adequate to support its approval as well as support its labeling (Recommendation from the original review attached).

It appears that the applicant received Dr. Gordin's comments from his original Biopharmaceutics Review. On January 27, 1992, the applicant submitted a response to address the formulation issue, i.e., whether a 3-6 D-xylopyranose unit polymer or the 17 D-xylopyranose unit polymer was (in the formulation) used in 3 bio-studies. The reviewing chemist for HFD-160 was requested to review this material as to the validity of the applicant's response. However, a review can not be located which addresses the validity of the applicant's response. In addition, it seems that the applicant did not respond to the remainder of Dr. Gordin's comments.

On January 27, 1993 (Stamp Date), The Division of Medical Imaging and Radiopharmaceutical Products issued a first "Not Approval" letter to the applicant. In this letter, under Biopharmaceutical heading, the following statement was conveyed to the applicant:

"The bio-data submitted has not adequately described the bioavailability/pharmacokinetics of Pentosan Polysulfate (PPS) in order to comply with 21 CFR 312.21 and is not adequate to support its approval as well as support its labeling. Please contact Dr. Daniel Gordin of the Division of Biopharmaceutics at (301) 443-3520 to discuss further requirements and study protocol designs."

On July 7 and 20, 1993, the applicant submitted a new protocol (Urinary Concentration-Controlled Trial of Elmiron) and resubmitted limited dissolution data available for different Elmiron capsule formulations use in the two efficacy clinical studies, respectively. In Dr. Gordin's review, he indicated that the applicant did not use the to-be-marketed capsule formulation in 3 bio-studies, and the sponsor's resubmitted dissolution information was found to be inadequate. In addition, Dr. Gordin stressed that in the urinary concentration-controlled trial, patients should be administered with the to-be-marketed formulation in order to avoid a bioequivalence issue because of this product's very low systemic bioavailability (Dr. Gordin's review attached: Stamp Date 10/13/1993).

On October 28, 1994 (Stamp Date). The Division of Medical Imaging and Radiopharmaceutical Products issued a second "Not Approval" letter to the applicant. In this letter, under Biopharmaceutical heading, the following statements were conveyed to the applicant; however, it is not clear if a separate IND letter was sent to the applicant regarding urinary concentration-controlled trial protocol and related issues (#b):

- a. The to-be-marketed formulation should, if possible, be used in the new clinical study in order to avoid a bioequivalence issue.
- b. Your July 7, 1993, amendment included a new protocol (IX 106-063A) synopsis to address the bioavailability and pharmacokinetic data which were mentioned in our January 27, 1993, not approval letter. This protocol and related issues will be addressed in a separate IND letter."

RECOMMENDATION:

Overall comment: Not Approval from a Biopharmaceutics Perspective

The applicant submitted no additional pharmacokinetic information in the amendment. This reviewer concurs with the previous decision made by the primary pharmacokinetic reviewer, Dr. Daniel Gordin, that bio-data submitted has not adequately described the bioavailability/pharmacokinetics of Pentosan Polysulfate (PPS) in order to comply with 21 CFR 312.21 and is not adequate to support its approval as well as support its labeling.

General comments:

- A. Phase IV human study: The applicant should commit to perform, post-approvable, human pharmacokinetic studies to define PPS's pharmacokinetic and metabolic profile. This reviewer recommends that the sponsor should be given a time-line to submit the protocol (with to-be-marketed formulation), e.g., within 30 - 60 days after the official correspondence to the sponsor.
- B. Drug labeling: Under CLINICAL PHARMACOLOGY section, the applicant should add subsections,

C. With respect to pharmacokinetic information provided in Elmiron's Investigative Brochure, the applicant needs to elaborate or submit the supporting data (underlined) to the following items:

1. Page 15, Table 4: Clinical Pharmacokinetic Studies

There are 7 investigators listed in the table, however, this reviewer is observant of 3 pharmacokinetic studies submitted by the applicant :

a. Fellstrom (Study 6-1); b. Greenslade (Study 6-2); c. Kummer (Study 6-3).

Were studies conducted by McGregor, Jallad, Losonczy, and Forestier sponsored by the applicant, and individual data submitted to the agency?

2. Page 16, first paragraph,

"Total body clearance for ^3H -PPS ranged from mL/min (mean = 191)..." - supporting data needed

"...Unchanged PPS accounted for 20-30% of the administered dose...These data suggested that 40% of the orally administered dose was absorbed..." - supporting data needed

3. Page 16, second paragraph,

"During the 120 hour collection period the majority of the administered radioactivity was recovered in the feces and urine (83.7 ± 11.6%) with the feces..."

The applicant stated that peak plasma concentration was reached in approximately 1 hour of dosing. According to Study 6-2 (Greenslade), Table 8.5 titled "Plasma concentrations of non-volatile radioactivity in male volunteers", ^3H -SP54 peaked at 1.0 hour and at 4.0 hour in male subjects. The applicant should re-evaluate the data.

The applicant stated that "...There was no evidence that the pharmacokinetics of ^3H -PPS differed between dose levels of 2 and 10 mg/kg." The applicant should provide further explanation of the above statement, since n = 1 was used in each dosing level, i.e., 2, 5, or 10 mg/kg dose. Is the statement statistically valid, i.e., was a trend observed?

4. Page 16, third paragraph,

The information reported by MacGregor needs to be verified. The applicant should submit the study report with individual data and assay validation.

5. Page 16, last paragraph, (continued on Page 17)

"...The bioavailability of PPS was estimated to be 0.5-1%. Urinary excretion after iv and oral administrations of PPS were 3.32 ± 0.8 mg/24h and 230 ± 94 µg/24h respectively."

"After 3 weeks of oral administration plasma levels of PPS ranged from µg/mL." - The applicant needs to indicate that these are "trough" plasma levels.

"It was concluded that the main route of metabolism for PPS is degradation, probably by desulfation in the liver. Urinary inhibition of calcium oxalate crystals growth was increased

with PPS administration; however, this increase (magnitude ?) was approximately the same after IV and PO administration. - Supporting data needed to indicate metabolism, i.e., desulfation in the liver.

6. Page 17,

The information reported by Jallad needs to be verified. The applicant should submit the study report with individual data and assay validation.

7. Page 17 and 18,

The efficacy information reported by Jallad, Losonczy, and Forestier needs to be verified by the reviewing medical officer.

David J. Lee 2/5/96

David J. Lee, Ph.D.
Pharmacokineticist
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics
8

Concurrence:

Ruth E. Stevens 2/5/96

Ruth E. Stevens, Ph.D.
Pharmacokineticist, Group Leader
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: HFD-160 NDA 20-193
HFD-160 DIV FILE
HFD-160 /MO/LPASERCHIA (1X)
HFD-160 /CSC/SCUSACK (1X)
HFD-160 /OCPB/RSTEVENS (2x)
HFD-160 /OCPB/DLEE (1x)
HFD-860 /OCPB/HMALINOWSKI (1X)
HFD-870 /OCPB/MLCHEN (1X)
HFD-880 /OCPB/NFLEISCHER (1X)
HFD-850 /OCPB/LLESKO (1X)
HFD-850 /OCPB/CHRON., DRUG, REVIEWER (3X)
HFD-340 /VISWANATHAN (1X)
HFD-205 FOI

The sponsor has obtained orphan status for this product. It still is unclear to the Division of Biopharmaceutics what the sponsor's assay is actually measuring, therefore all data regarding pharmacokinetic parameters are in question.
Ruth Stevens 2/5/96

FEB 25 1992

PENTOSAN POLYSULFATE SODIUM
Elmiron - 100 mg Capsule
NDA 20-193 / 1 - C
Reviewer: M. Daniel Gordin, Ph.D.

BAKER CUMMINS
MIAMI, FL
Submission Date
June 11, 1991

TYPE OF REVIEW: REVIEW OF A NEW MOLECULAR ENTITY

I. BACKGROUND AND SYNOPSIS:

Pentosan Polysulfate (PPS) is indicated for the treatment of interstitial cystitis and works by adhering to the exposed mucosal layer of the bladder epithelium thereby decreasing the diffusion of urine components through the bladder wall. It was granted an Orphan Status for the treatment of interstitial cystitis in August 1985. Three bio-studies were submitted by the sponsor which were sponsored by the manufacturer of the drug substance, and did not use the to-be-marketed capsule. Chemically, PPS is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative which chemically and structurally resembles glycosaminoglycans (Fig 1) and has a molecular formula of $[C_5H_7O_6(SO_3Na)]_n$ where $n=17$ and molecular weight of 5700.

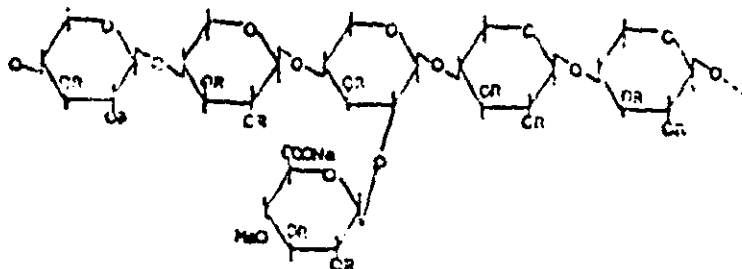


Fig 1. Pentosan Polysulfate

II. RECOMMENDATION:

Based upon the review of the submitted pharmacokinetic information, the Division of Biopharmaceutics (DB) is of the opinion that the bio-data submitted in NDA 20-193 has not adequately described the bioavailability/pharmacokinetics of Pentosan Polysulfate in order to comply with 21 CFR 320.21 and is not adequate to support its approval as well as support its labeling. This is based on the following reasons:

1) The sponsor submitted 3 bio-studies which i) used a compound designated as SP54 which appears to be a shorter chain macromolecule of only 3-6 linked D-xylopyranose units as compared to molecular structure described in this NDA for PPS which is 17 D-xylopyranose units long; as a result, the kinetic information contained in this application may not be applicable to the PPS molecule ii) did not use the to-be-marketed capsule formulation, state how these formulation(s) compare to the capsule formulation to-be-marketed, or provide comparative dissolution results of these formulations iii) did not have validation of the assay used for the analysis of pentosan polysulfate iv) did not employ a sufficient number of study subjects to draw conclusions of the kinetics of PPS e.g. Studies 6-1, 6-2, and 6-3 used only 8, 3, 8 subjects, respectively and lastly v) did not characterize the kinetics of PPS using the proposed 100 mg dose or tid dosing regimen administered 1 hr before or 2 hrs after a meal. In conclusion, these 3 bio-studies appear to be pilot studies and did not adequately describe the kinetics of the to-be-marketed 17 chain PPS molecule as well as relate to the to-be-marketed capsule formulation under its proposed dose and dosing regimen.

2) Two different capsule formulations which differ by micro-crystalline cellulose content (80 mg vs 123 mg) (manufactured by) were used in the 2 pivotal clinical studies E-001 and E-002. The formulation with the 123 mg amount will be the to-be-marketed capsule formulation; however, bioavailability data comparing the 2 formulations was not submitted and the dissolution results submitted by the sponsor comparing the two clinical formulations is not adequate to make a comparison since only 2 capsules were used from each lot. It was learned from Ms. Jane Hsiao of Baker Cummins (January 14, 1992) that clinical study E002 was a stronger study statistically which may be due to formulation effect. In order to determine this, a bioequivalency study comparing the 2 formulations would be required; however, it was also learned that the 2 lots used in the pivotal clinical studies have expired. Therefore, a comparison between formulations is not feasible. As a result, there is only 1 pivotal clinical study that has used the to-be-marketed capsule formulation.

3) The sponsor submitted dissolution profiles on a mean of only 2 capsules from each of the 2 clinical lots (a description of the dissolution methodology was not provided). These dissolution

results are not adequate for meeting the DB dissolution guidelines which requires dissolution profiles for 12 dosage units in 3 dissolution media (Water, Simulated Intestinal Fluid, and Simulated Gastric Fluid) plus a pH solubility profile.

4) The sponsor did not submit a food effect study. In the 3 bio-studies, PPS was administered after fasting which continued for 4 hrs, and the availability of unchanged PPS in the urine was shown to be only 3% or less. A concern is that the bioavailability of PPS may be worse under nonfasting conditions. A food effect study would be required to evaluate this possibility.

5) A study in patients with liver disease was not submitted. PPS is desulfated by both the liver and spleen. A bio-study to determine the kinetics of PPS in patients with liver deficiency is needed if this drug is to administered to such patients.

6) Discussions with the Reviewing MO of HFD-160 revealed that the oral administration of PPS was effective in only 10-15% of the patients studied. The effectiveness of orally administered PPS for interstitial cystitis is dependent upon sufficient amounts of unchanged PPS being absorbed from the GI tract and its subsequent excretion as unchanged PPS into the bladder where it then binds to the exposed mucosal epithelium. The results of the most favorable bio-study showed that following multiple dose administration of 150 mg PPS capsules tid for 7 days followed by 150 mg of ³H-PPS, 11% of the total radioactivity was excreted in the urine which consisted of a mean of 3% as unchanged PPS [(N=4) 3.9%, 2.5%, 4.2% and 1.4%]. Therefore, the low efficacy of PPS following oral administration may be due to the poor absorption of unchanged PPS from the GI resulting in sub-therapeutic amounts of unchanged PPS in the bladder. Since PPS is a large molecular weight compound (MW 5700), this result of poor systemic bioavailability following oral administration is not unexpected. It is possible that the current 100 mg dose and/or tid dosing regimen are not sufficient to contribute adequate amounts of unchanged PPS in the bladder to be therapeutic. The sponsor stated in the NDA that both the dose and dosing regimen were based primarily on anecdotal information. In order to determine if a more optimum dose and dosing regimen can be found to deliver greater amounts of unchanged PPS to the bladder, it is suggested that new clinical studies be performed using higher doses and/or shorter duration of drug administration such as qid prior to approval of this product (if this was not already performed under Phase I or II).

Please convey to the sponsor that if they intend to proceed with further development of this NDA, then they should contact the Division of Biopharmaceutics to discuss further requirements and study protocol designs.

M. Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

Biopharm Day January 22, 1992; Drs. J. Collins, H. Malinowski,
T. Ludden, P. Hepp, N. Fleischer and J. Hunt

FT Initialed by Nicholas Fleischer, Ph.D. *N. Fleischer 2/24/92*

cc: NDA 20-193, HFD-160, HFD-426 (Gordin and Fleischer), Drug,
Chron, Reviewer, and HFD-19 (FOI).

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OCT 13 1993

Div
PENTOSAN POLYSULFATE SODIUM
Elmiron - 100 mg Capsule
NDA 20-193
Reviewer: M. Daniel Gordin, Ph.D.

BAKER CUMMINS
MIAMI, FL
Submission Date
July 7, 1993
July 20, 1993

I. BACKGROUND:

Pentosan Polysulfate (PPS) is indicated for the treatment of interstitial cystitis (IC) and acts by adhering to the exposed mucosal layer of the bladder epithelium. Three bio-studies were initially submitted by the sponsor in the original NDA which were sponsored by the manufacturer of the drug substance, and did not use the to-be-marketed capsule. Volume 3 of the July 7 submission contains summaries of journal articles pertaining to the kinetics of pentosan polysulfate and the results of 3 studies which were contained in the original June 1991 NDA which have previously been reviewed (Reviewed Stamp Date: 2/25/92); therefore, a review of this information has already been done. This submission does make note that the sponsor plans to conduct a Urinary Concentration-Controlled Trial. A synopsis of the study was submitted which will be reviewed.

Title: Urinary Concentration-Controlled Trial of Elmiron

Objective: To determine whether there is a relationship between urinary concentration (the drug's site of action i.e. within the bladder) and improvement in symptoms of interstitial cystitis (IC).

Design:

This will be a randomized, 3 center concentration controlled study of 45 patients with IC. Patients will be assigned to the following 3 target urine drug concentrations 1 - 2 ug/ml; 3 - 15 ug/ml; and 16 - 30 ug/ml. There will be a 1-week lead in period for each patient followed by 50 mg tid for 7 days. On day 8, the first AM void will be collected and all subsequent urine collected as well. All urine samples will be analyzed for drug. Based on the first AM void, the investigators will adjust the dose of drug by frequency of dosing and/or amount per dose so that the assigned drug levels are achieved and maintained. Patients will continue to received the individualized dose for 6 months. The adjustment of dose is to be based on the values observed from the day 8 urine sample and subject's weight, height, and body build and level of renal function.

Endpoints:

The primary endpoint will be global evaluation by the patient. The secondary endpoints include global evaluation by the investigator, improvement in pain, quality life assessments (# of days missed from work, unexpected clinic visits, etc.)

COMMENTS:

Since this was an incomplete protocol, a full review cannot be done at this time; however the following points are suggested for the sponsor to consider as they fully develop this protocol.

1) The endpoints suggested by the sponsor are all subjective measures. If it is possible, at least one objective endpoint that can be measured as the primary endpoint should be included.

2) If the global assessments mentioned by the sponsor are a patient questionnaire, it should be validated prior to use.

3) Although subject inclusion was not mentioned in this synopsis, females and elderly should be included.

4) This synopsis protocol mentions that dosage adjustment will be based on the Day 8 urine void until the patient achieves and maintains the desired level. A time schedule for checking subsequent urine samples for drug levels needs to be included.

5) Elmiron works by binding to exposed epithelium. As a result, the presence of food to which it may bind may theoretically decrease its absorption from the GI tract. Since a food effect study was not conducted during Phase I development, it is suggested that prior to the new clinical study, the sponsor should investigate a possible food effect in order to determine the optimum dosing regimen i.e. with or without food. However, if the sponsor intends to dose on an empty stomach, then this issue may not have to be addressed through a control Phase I study. Consequently, the sponsor should insure that the administration of Elmiron to the patients in this new clinical study be controlled for time of dose relative to meals for all patients. This information could then be used in the package insert for dosing instructions.

6) If possible, a placebo arm should be added. At the very least, patients could be on placebo up to Day 8 (at which dosage adjustments are made for active drug) and then maybe until the first questionnaire is obtained.

Contained in the July 20, 1993 submission is limited dissolution data available for different Elmiron capsule formulations used in the two clinical studies. The following comments were noted in the Biopharmaceutics review (2/25/92) of the NDA:

1) Two different capsule formulations which differ by micro-crystalline cellulose content (80 mg vs 123 mg) (manufactured by _____) were used in the 2 pivotal clinical studies E-001 and E-002. The formulation with the 123 mg amount will be the to-be-marketed capsule formulation; however, bioavailability data comparing the 2 formulations was not submitted and the dissolution results submitted by the sponsor comparing the two clinical formulations is not adequate to make a comparison since only 2 capsules were used from each lot. It was learned from Ms Jane Hsiao of Baker Cummins (January 14, 1992) that clinical study E002 was a stronger study statistically which may be due to a formulation effect. In order to determine this, a bioequivalency study comparing the 2 formulations would be required; however, it was also learned that the 2 lots used in the pivotal clinical studies have expired. Therefore, a comparison between formulations is not feasible. As a result, there is only 1 pivotal clinical study that has used the to-be-marketed capsule formulation.

2) The sponsor submitted dissolution profiles on a mean of only 2 capsules from each of the 2 clinical lots (a description of the dissolution methodology was not provided). These dissolution results are not adequate for meeting the DB dissolution guidelines which requires dissolution profiles for 12 dosage units in 3 dissolution media (Water, Simulated Intestinal Fluid, and Simulated Gastric Fluid) plus a pH solubility profile.

RECOMMENDATION:

Pertaining to the July 7, 1993 submission, please note Comments 1-6. The Reviewing Medical Officer should review this protocol for safety and whether Comments 1-6 are valid to the convey to the sponsor.

Pertaining to the July 20, 1993 submission, the sponsor resubmitted the dissolution information that was found to be inadequate. Regardless, since a new clinical study is going to be conducted, it should be stressed to the sponsor that they should make sure that patients are dosed with the to-be-marketed formulation in order to avoid a bioequivalence issue at the end due to the difficulty in determining bioequivalence because of this product's very low systemic bioavailability.

Please convey to the sponsor the following statement:

"It is stressed that the to-be-marketed formulation for Elmiron be utilized for the conduct of the new clinical study (Titled: Urinary Concentration-Controlled Trial of Elmiron) in order to avoid a bioequivalence issue between a clinical formulation and the to-be-marketed formulation."



M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by John P. Hunt October 6, 1993

FT Initialed by John P. Hunt JPH 10/8/93

cc: NDA 20-193, HFD-160, HFD-426 (Gordin), Drug, Chron, Reviewer, and HFD-19 (FOI).

\160\Pentosan.79 September 15, 1993 October 7, 1993

PENTOSAN POLYSULFATE SODIUM
Elmiron - 100 mg Capsule
NDA 20-193
Reviewer: M. Daniel Gordin, Ph.D.

BAKER CUMMINS
MIAMI, FL
Submission Date
January 27, 1992

BACKGROUND

Pentosan Polysulfate (PPS) is indicated for the treatment of interstitial cystitis. In the Biopharmaceutics review of NDA 20-193 (Review Stamp Date: February 25, 1992), it was noted that a compound designated as SP54 was used which was described in the 3 bio-study reports as a 3-6 D-xylopyranose unit polymer compared to the 17 D-xylopyranose unit polymer described in the NDA Chemistry section for the PPS drug the sponsor intends to market. Therefore, a concern was raised that the kinetic information obtained on the shorter chain polymer may not be applicable to the longer chain to-be-marketed PPS polymer. The sponsor was requested to respond to this apparent discrepancy.

In this submission, the sponsor has responded with a discussion on polymer chemistry. It is requested that the Chemist for HFD-160 review this material as to the validity of the sponsor's response as to whether the drug product designated as SP54 which was used in the NDA bio-studies for Pentosan Polysulfate is the same drug which the sponsor intends to market.

M. Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by Nicholas Fleischer, Ph.D.
FT Initialed by Nicholas Fleischer, Ph.D.

N. Fleischer 8/28/92
N. Fleischer 8/28/92

cc: NDA 20-193, HFD-160, HFD-426 (Gordin and Fleischer), Drug, Chron, Reviewer, and HFD-19 (FOI).

\160\Pentosan.Con

III. SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS:

A. BIOAVAILABILITY:

Since the effectiveness of PPS is dependent upon sufficient amounts of unchanged PPS being absorbed following oral administration and its subsequent excretion as unchanged PPS into the bladder, the availability of PPS in the bladder is the measure of "bioavailability". From Study 6-3, a multiple dose study in which 150 mg PPS capsules tid (450 mg/day) was administered for 7 days followed by a 150 mg capsule of radiolabelled PPS showed that approximately 90% (range 84-104) of total radioactivity was recovered from both urine and fecal samples. Of this, approximately 11% $\pm$ 2.5 (range 9-16) of total radioactivity was excreted in the urine after oral dosing which consisted of a mean of 3% $\pm$ 1.3 of the dose excreted as unchanged PPS (individual subject data: 3.9%, 2.5%, 4.2% and 1.4%) as determined by tlc.

B. FORMULATION and BIOEQUIVALENCE:

Table 1. The 100 mg PPS capsule formulations used in Clinical Studies E-001 and E-002 (Production Size Batch

	E-001	E-002
	Lot No. KI80245	Lot No. 9086-7
Pentosan Polysulfate Sodium	100 mg	100 mg
Microcrystalline Cellulose	mg	mg
Magnesium Stearate	- <u>mg</u>	<u>mg</u>
TOTAL CAPSULE FILL WEIGHT	mg	mg
Batch Size		

Two different capsule formulations of 100 mg PPS were used in Clinical Studies E-001 and E-002 (Table 1). As shown, there is approximately a 50% difference in the microcrystalline cellulose amount between the two formulations. The diluent, microcrystalline cellulose, is used to facilitate disintegration of a dosage form, which would lead to faster drug dissolution, leading to faster drug absorption, and ultimately, leading to faster onset of drug effect. The NDA states that the proposed formulation for marketing will be Lot 9086-7 which was used in clinical study E-002. According to the sponsor, this study showed the greatest drug efficacy as opposed to Lot No. KI80245. A dissolution study (for which the methodology was not described and used only 2 capsules which is not sufficient for a definitive comparison) compared the 2 capsule formulations. The results show that at the 10 min timepoint, the 123 mg of microcrystalline cellulose formulation was more than 90% dissolved compared to 60% for the other formulation which was not $\geq$ 90% dissolved until the 20 min timepoint. As a result, the clinical difference seen between the 2 clinical studies may be due to the differences between the 2 capsule formulations. A bioequivalency study between the formulations was not performed. Therefore, at this time, there is only 1 pivotal clinical study that has used the to-be-marketed capsule formulation.

C. FOOD EFFECT:

A food effect study was not performed.

D. PHARMACOKINETICS:

According to the sponsor, following oral dosing the detection of PPS plasma levels was problematic due to the lack of a sensitive assay; therefore, kinetic parameters of C_{max}, AUC, t_{max}, and half-life following an oral dose are lacking.

E. METABOLISM:

From Study 6-3, following 150 mg PPS capsules tid (450 mg/day) for 7 days prior to the oral administration of 150 mg radiolabelled capsule, approximately 90% (range of total radioactivity was recovered from both urine and fecal samples. Of this, approximately 11% ± 2.5 (range of total radioactivity was excreted in the urine after oral dosing, and a mean of 3% ± 1.3 of the dose was renally excreted as unchanged PPS.

F. DOSE PROPORTIONALITY:

Only a 100 mg dosage strength capsule will be marketed and only a 100 mg tid dosage regimen is to be approved; therefore, dose proportionality is not an issue.

G. SPECIAL POPULATIONS:

Studies in special population such as renal patients, hepatic patients, or the elderly were not performed.

H. DRUG INTERACTIONS:

Drug interaction studies were not performed.

I. PHARMACODYNAMICS:

A PK/PD relationship was not done nor can a relationship be established due to the absence of PK data.

VI. REVIEW OF THE PHARMACOKINETICS STUDIES

TITLE: No title (STUDY 6-1)

INVESTIGATOR: No investigator stated

DESIGN:

Only a summary of the study was submitted. This was a multiple dose, 2-treatment, nonrandomized study involving 8 healthy males who in Treatment 1 after an overnight fast received on Study Day 1 an iv bolus dose of 40 mg ¹²⁵I-PPS. One week later in Treatment 2, a single oral dose of 4x100 mg PPS (SP54) capsules was administered followed by qd AM dosing for 21 days of 4x100 mg PPS not-to-be-marketed capsules. Fasting continued 4 hrs after dosing.

Blood samples were taken after the iv dose at 0, 15, 30 min, 1, 2, 4, 6, 8, 10, and 24 hrs.

Samples after the single oral dose were obtained at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hrs. Pre-dose samples were obtained on Study Days 20 and 21.

Urine was collected at 0-2, 2-4, 4-6, 6-8, 8-10, and 10-24 hrs after dosing on Days 21 and 22.

RESULTS:

Following an iv bolus dose of PPS, plasma concentrations were fitted to a two-compartment model. The mean elimination half-life of PPS following the iv dose was determined to be 24.1 mins ± 10.8. The mean renal clearance of PPS was 4.2 ± 1.2 ml/min.

After a single 400 mg oral dose, plasma levels of PPS were not detectable. The urinary excretion of unchanged PPS over 24 hrs showed less than 1% (range %) of the oral dose renally excreted in all 8 subjects. On Days 21 and 22 of multiple dose, the trough plasma concentration of PPS were around 0.03 µg/ml. The urinary excretion of absolute amount of PPS over 24 hrs for both Days 21 and 22 showed a great deal of inter- as well as intra-subject variability. In subjects 3 and 6, there were no detectable urine levels. In subject 5, urine levels decreased from µg on day 21 to 0 on day 22, and in subject 8, urine levels increased from µg on Days 21 and 22 (tables are attached).

COMMENTS:

1. It is stated in the study design that ¹²⁵I-PPS was administered; however, it is not clear where the ¹²⁵I was tagged since iodine is not within the molecular structure of PPS.

2. According to the sponsor, the detection of plasma levels of PPS following a single oral dose was problematic due to the lack of a sensitive assay. For analysis, a competitive binding assay was used which, according to the reference, is sensitive down to 10 ng/ml. No further assay validation was submitted.

3. The results of this study showed that following 22 days of qd dosing of 4x100 mg capsules (which is not the proposed dose or regimen), 2 out of the 8 subjects (25%) had no detectable PPS urine concentrations on Days 21 and 22 and that renal excretion of PPS is highly variable (subject 5 went from μg on Day 21 to on Day 22).

4. The availability of PPS in the bladder determined from the amount of drug excreted unchanged in the urine was determined to range from $\%$. It can be concluded that oral PPS is poorly absorbed, and if efficacy of PPS is questionable, then this may be due to the poor bioavailability of PPS.

TITLE: PENTOSAN POLYSULFATE: A KINETIC STUDY IN MAN AFTER ORAL ADMINISTRATION (STUDY 6-2)

INVESTIGATOR:

STUDY PERIOD: 1983

DESIGN:

3 healthy subjects were administered a single oral dose of randomly labelled ³H-PPS at dose levels of either 2, 5, or 10 mg/kg (150.4, 314.9, and 692.9 mg, respectively) after an overnight fast. The oral dose consisted of purified ³H-PPS (SP 54) which was dissolved in distilled water, freeze dried, and then packed in a hard gelatine capsule. Serial samples of blood, urine, and feces were collected for 120 hrs post-dose. The absorption and elimination of radioactivity were measured and any metabolites present in the urine were examined by gel filtration chromatography.

RESULTS:

Table 1. The overall recovery of total and non-volatile radioactivity in 3 male subjects at 3 doses collected over 120 hrs as percent of dose.

	<u>150.4 mg</u>	<u>314.9 mg</u>	<u>692.9 mg</u>
Urine	3.3	3.5	3.5
Fecal extracts	5.0	9.7	27.9
Fecal residues	61.4	76.5	59.5
Total (%)	69.7	89.7	90.9

fecal extracts refers to fractions of radioactivity measured in the fraction of feces solubilized in a mixture of methanol:water, the radioactivity remaining in the solid fraction was considered as fecal residue.

COMMENTS:

1. The sponsor states that quantitation of blood and plasma concentrations of radioactivity proved difficult because of low plasma levels. The recovery of radioactivity after a single dose was 3.3 to 3.5% in urine and 5 to 27.9 for the fecal extract and 59.5 to 76.5 for fecal residue (Table 1). The sponsor states that the examination of urine by gel filtration chromatography indicated virtually no unchanged ³H PPS was present in the urine after apparent degradation to lower molecular weight product(s). The results of this study indicate very poor absorption of PPS following a single oral dose, and the radioactivity detected in urine were metabolites of PPS.

TITLE: ABSORPTION, DISTRIBUTION, AND EXCRETION OF ³H PPS AFTER PARENTERAL AND ORAL APPLICATION (STUDY 6-3)

INVESTIGATORS:

DESIGN:

This was a 2-way crossover study involving 8 healthy male volunteers (age 45-65). In treatment 1, subjects received 150 mg PPS (SP54) capsules (Batch 680096) tid (450 mg total dose/day) for 7 days prior to the oral administration of randomly labelled 150 mg ³H PPS capsule. In treatment 2, following a 3 week washout, subjects received a single 75 mg dose of PPS infused for 30 min.

Blood samples were collected on the last day following the oral dose at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 16, 24, 36, 48, 72, 96, 120, and 144 hrs post dose.

Blood samples were collected ^{after the start of} the parenteral dose at 0, 0.1667, 0.333, 0.5, 0.55, 0.667, 0.75, 0.833, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 14, 24, 36, 48, 72, 96, 120 and 144 hrs post dose.

Urine was collected following both oral and parenteral doses at 0-2, 2-6, 6-12, 12-24, 24-36, 36-48, 48-62, 62-72, 72-96, 96-120, 120-144 hr intervals.

Fecal samples were collected daily for 7 days.

RESULTS:

Table 1. The renal and fecal excretion of PPS total radioactivity following 150 mg PPS tid for a period of 7 days as percent of dose.

<u>Subject</u>	<u>Urine (0-144)</u>	<u>Feces (0-144)</u>	<u>Total</u>
	16	68	84
	12	92	104
	11	85	96
	9	82	91
	14	90	104
	10	49	59
	9	78	87
	9	82	91
Mean	11	78	90

COMMENTS:

1. Following 150 mg PPS tid (450 mg/day) for 7 days and then an oral dose of 150 mg radiolabelled drug, approximately 90% (range 84-104) of total radioactivity was recovered from both urine and

NDA 28-193

4 OF 7

fecal samples (Table 1). Of this, approximately $11\% \pm 2.5$ (range $\%$) of total radioactivity was excreted in the urine after oral dosing. In 4 of the 8 subjects, the urinary excretion of unchanged PPS was determined using exclusion chromatography and tlc detection to discriminate unchanged PPS from total radioactivity. Of the 11% total radioactivity in the urine following oral dosing, a mean of $3\% \pm 1.3$ of the dose was renally excreted as unchanged PPS in 4 subjects (individual subject data: $\%$).

3. Following parenteral infusion, the fecal and urinary excretion of total radioactivity was 4% (range $\%$) and 27% (range $\%$) of the dose compared to 78% (range $\%$) and 11% (range $\%$) of the dose after oral administration. The total radioactivity recovered following oral dosing was 90% and only 30% following parenteral infusion. The sponsor speculates that this low recovery following infusion may be due to the adsorption of PPS to macromolecular structures within the body or its use for anabolic processes within the body due to its similar structure to other glucosaminoglycans.

The following journal articles were submitted and provide useful information, but the validity of the information and data cannot be verified:

Macgregor, I.R. et.al. Metabolism of Sodium Pentosan Polysulfate in Man - Measured by a New Competitive Binding Assay- Comparison with Effects upon Anticoagulant Activity, Lipolysis and Platelet Proteins Thromb Haemostas; 53: 411, 1985.

Macgregor, I.R. et.al. Metabolism of Sodium Pentosan Polysulfate in Man Measured by a New Competitive Binding Assay- Comparison with Effects upon Anticoagulant Activity, Lipolysis and Platelet Proteins Thromb Haemostas; 51(3): 321, 1984.

Forestier, F. Absence of Transplacental Passage of Pentosan During Mid Trimester of Pregnancy Thromb and Haemostas; 56 (3): 247, 1986.

STUDY 6-1

1986-04-03

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Table I. →

Volunteers characteristics.

Subject	Sex	Age (yr)	Weight (kg)	Height (cm)
	M	41	98	175
	M	30	68	171
	M	43	99	186
	M	38	64	178
	M	46	80	179
	M	37	64	181
	M	34	67	180
	M	30	92	187

1986-04-03

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Table II

Disposition of pentosan polysulphate after intravenous administration (40mg).

Subject	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (hr)	V_1 (l/kg)	$V\beta$ (l/kg)	V_{ss} (l/kg)	Cl_p (ml/min)	Cl_R (ml/min)
Mean $\pm$ S.D.	24.5 $\pm$ 4.4	24.1 $\pm$ 10.8	0.05 $\pm$ 0.01	1.25 $\pm$ 0.38	0.67 $\pm$ 0.28	49.9 $\pm$ 6.6	4.2 $\pm$ 1.2

1986-04-03

~~25~~

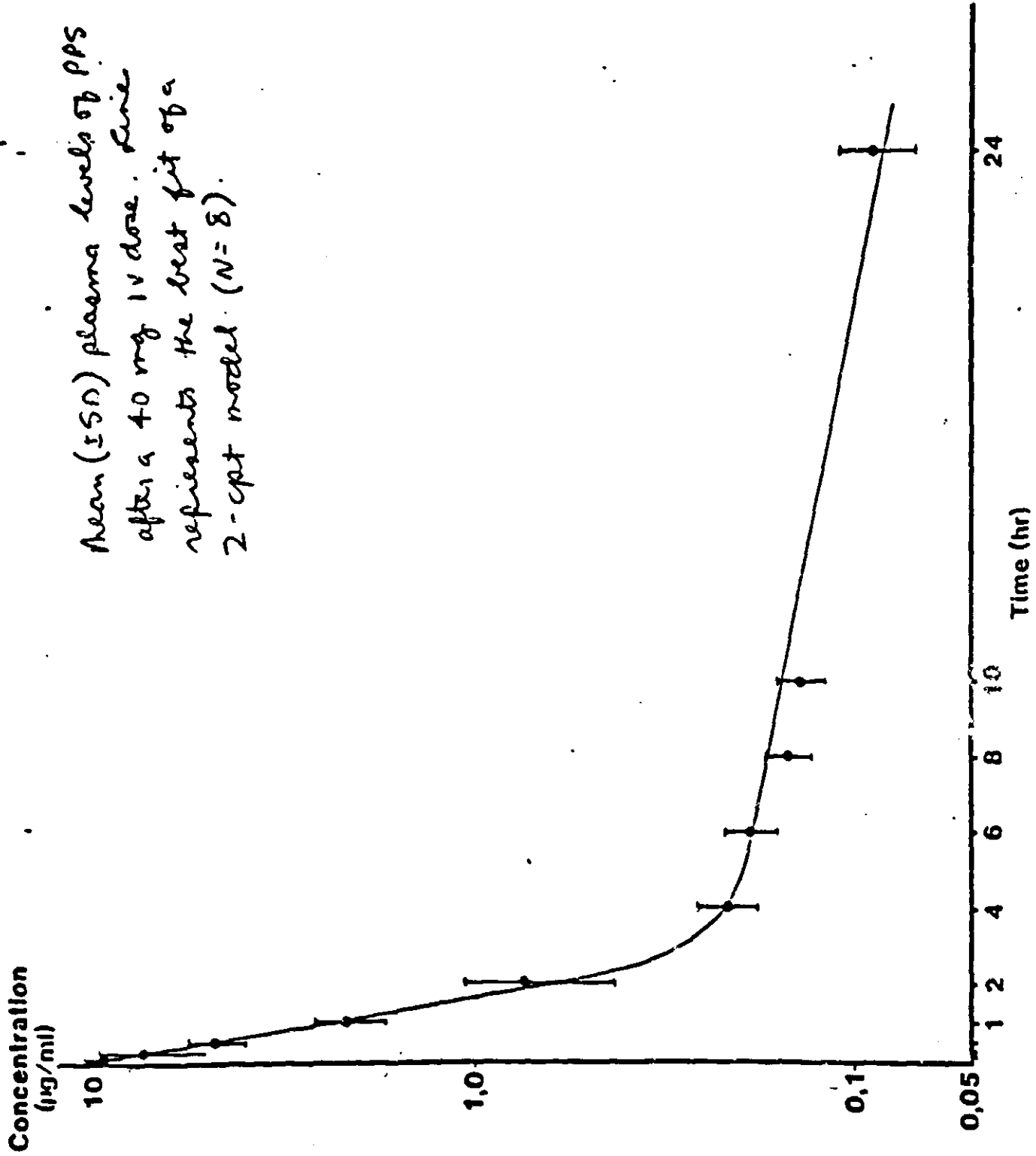
Table III

Plasma concentration ($\mu\text{g/ml}$) of pentosan polysulphate (thorough levels) on 2 consecutive days during continuous oral administration of 400mg daily.

(min values)

Subject	Day 20	Day 21
	0.03 ^{3rd}	0.03
	0.03	0.03
	0.02	0.03
	0.05	0.04
	0.03	0.03
	0.03	0.03
	0.03	0.04
	0.04	0.03

Mean (SD) plasma levels of PPS
 after a 40 mg IV dose. Line
 represents the best fit of a
 2-comp model (N=8).



Plasma concentrations ($\mu\text{g}/\text{ml}$) of PPS at different times after 40 mg i.v. in 8 healthy volunteers.

Subject and two i.v. tests (1+2)	0'	5'	15'	30'	1h	2	4	6	8	10	24
1		.08	.25	.5							
2											
1											
2											
1											
2											
1											
2											
1											
2											
1											
2											

Urinary excretion (μg) of PPS during 24hrs after i.v. administration of 40 mg in 8 healthy volunteers.

Subject and two i.v. tests (1+2)	Blank ($\mu\text{g/ml}$)	0-2 (μg)	2-4 (μg)	4-6 (μg)	6-8 (μg)	8-10 (μg)	10-24 (μg)
1							
2							
1							
2							
1							
2							
1							
2							
1							
2							
1							
2							

Plasma concentration ($\mu\text{g/ml}$) of PPS after 400mg (single dose) orally to 8 healthy volunteers.

Subject Blank 15' 30' 60' 2 3 4 6 8 10 24

Urinary excretion (μg) of PPS during 24 hours after p.o. administration of 400mg in 8 healthy volunteers.

400.000 mg

Subject	Blank ($\mu\text{g/ml}$)	0-2 (μg)	2-4 (μg)	4-6 (μg)	6-8 (μg)	8-10 (μg)	10-24 (μg)

%

%

%

%

%

%

%

%

Plasma concentration ($\mu\text{g/ml}$) of PPS (through levels on 2 consecutive days during continuous oral administration of 400 mg daily. At least 3 weeks treatments.

Subject	Day 21	Day 22
	0.03	0.03
	0.03	0.03
	0.02	0.03
	0.05	0.04
	0.03	0.03
	0.03	0.04
	0.04	0.03

Urinary excretion (μg) of PPS on 2 consecutive days during continuous oral administration of 400 mg daily. At least 3 weeks treatments.

Subject	Day 21	Day 22	<u>Total</u>
	300	186	486
	195	189	
	0	0	
	265	284	
	431	0	
	0	0	
	271	284	
	0	548	

TABLE 0.1

Overall recovery of total and non-volatile radioactivity in male volunteers after an oral dose of ³H)-SP 54

Sample type	Collection period (hr)	Per cent of radioactive dose recovered		
		1M (2 mg/kg)	2M (5 mg/kg)	3M (10 mg/kg)
Urine	0 - 120	3.3 (3.4)	3.5 (3.5)	3.5 (3.4)
Faecal extracts	0 - 120	5.0 (5.5)	9.7 (10.4)	27.9 (27.5)
Faecal residues	0 - 120	61.4	76.5	59.5
Total		69.7 (70.3)	89.7 (90.4)	90.9 (90.4)

Total radioactivity given in parentheses.

TABLE A.2
 Urinary recovery of total and non-volatile radioactivity in male
 volunteers after an oral dose of (711)-SP 54

Collection period (hr)	Per cent of radioactive dose recovered		
	1H (2 mg/kg)	2H (5 mg/kg)	3H (10 mg/kg)
0 - 2	0.5 (0.6)	0.6 (0.6)	0.6 (0.6)
2 - 4	0.8 (0.8)	0.7 (0.7)	0.7 (0.7)
4 - 6	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
6 - 8	0.3 (0.3)	0.5 (0.5)	0.3 (0.3)
8 - 10	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)
10 - 12	0.2 (0.2)	0.2 (0.2)	NS (NS)
12 - 14	0.2 (0.2)	0.1 (0.1)	0.4 (0.4)
14 - 24	0.3 (0.3)	0.4 (0.4)	0.5 (0.4)
24 - 48	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
48 - 72	<0.1 (<0.1)	<0.1 (<0.1)	<0.1 (<0.1)
72 - 96	<0.1 (<0.1)	<0.1 (<0.1)	<0.1 (<0.1)
96 - 120	<0.1 (<0.1)	<0.1 (<0.1)	<0.1 (<0.1)
Total	3.3 (3.4)	3.5 (3.5)	3.5 (3.4)

NS = no sample.
 Total radioactivity given in parentheses.

TABLE B.3
Recovery of total and non-volatile radioactivity in faecal extracts
of male volunteers after an oral dose of ^{131}I -SP 54

Collection period (hr)	Per cent of radioactive dose recovered		
	1M (2 mg/kg)	2M (5 mg/kg)	3M (10 mg/kg)
0 - 24	1.6 (1.7)	3.9 (4.4)	10.2 (9.7)
24 - 48	2.8 (3.2)	4.9 (5.0)	15.7 (15.7)
48 - 72	0.4 (0.4)	0.9 (1.0)	2.0 (2.1)
72 - 96	0.2 (0.2)	<0.1 (<0.1)	<0.1 (<0.1)
96 - 120	N.D. (<0.1)	<0.1 (<0.1)	<0.1 (<0.1)
Total	5.0 (5.5)	9.7 (10.4)	27.9 (27.5)

Total radioactivity given in parentheses.
 N.D. = Not detected.

TABLE 8.4
 Recovery of non-volatile radioactivity in faecal residues of male
 volunteers after an oral dose of ¹³¹I)-SP 54

Collection period (hr)	Per cent of radioactive dose recovered		
	1H (2 mg/kg)	2H (5 mg/kg)	3H (10 mg/kg)
0 - 24	12.1	31.9	43.4
24 - 48	33.0	30.3	12.6
48 - 72	14.7	13.3	2.9
72 - 96	1.1	0.9	0.1
96 - 120	0.5	0.1	0.5
Total	61.4	76.5	59.5

TABLE 8.5
Plasma concentrations of non-volatile radioactivity in male volunteers
after an oral dose of ³H-SP 54

Sample time (hr)	Plasma conc. of radioactivity (ng equiv. of ³ H)-SP 54)		
	1M	2M	3M
0.00			
0.25			
0.50			
1.00			
1.50			
2.00			
3.00			
4.00			
6.00			
8.00			
12.00			
24.00			
48.00			
72.00			
96.00			
120.00			

N.D. = Not detected.
Limits of reliable detection for subjects
were and
ng equivalents ³H-SP 54 respectively.

STUDY 6-3

FINAL REPORT SP 54
NK/b - 37

Tab. 1: ANTHROPOMETRIC DATA OF VOLUNTEERS NO. 1 - 8
AND REPLACEMENT NO. 9

Vol. no.	Initials	Age (Y)	Weight (kg)	Height (cm)
1	L. J.	48	73	169
2	V. K.	56	66	180
3	H. H.	55	73	180
4	Sch. J.	59	78	172
5	U. H.	56	80	178
6	G. J.	45	80	184
7	B. H.	45	80	174
8	V. E.	51	73	174
9	K. U.	46	94	194
	mean	51	77	178
	SD	5.4	7.8	7.5
	c. v.	10.6	10.1	4.2
	min	45	66	169
	max	59	94	194

Tab. 19

URINARY EXCRETION OF SP 54 TOTAL RADIOACTIVITY

CAPSULE 150 MG
 VOLUNTEER 1-8. VALUES IN PERCENT OF DOSE/FRACTION

Zeit- Endpunkte	Prob. 01	Prob. 02	Prob. 03	Prob. 04	Prob. 05	Prob. 06	Prob. 07	Prob. 08	Mean	SD	SE
0.00									0.0000	0.0000	0.0000
2.00									0.6530	0.3975	0.1406
6.00									2.0455	0.9028	0.3192
12.00									2.1106	0.7096	0.2682
24.00									2.8987	0.8692	0.3073
36.00									1.5352	0.6804	0.2406
48.00									0.7508	0.4443	0.1679
60.00									0.6889	0.5071	0.1793
72.00									0.2610	0.1900	0.0672
84.00									0.4156	0.3029	0.1071
120.00									0.1785	0.0822	0.0291
144.00									0.0573	0.0218	0.0077

Tab. 20

CUMULATIVE URINARY EXCRETION SP 54 TOT. RADIOACT.

CAPSULE 150 MG
 VOLUNTEER 1-8. VALUES IN PERCENT OF DOSE CUMULATED

Zeit- Endpunkte	Prob. 01	Prob. 02	Prob. 03	Prob. 04	Prob. 05	Prob. 06	Prob. 07	Prob. 08	Mean	SD	SE
0.0									0.000	0.000	0.000
2.0									0.653	0.398	0.141
6.0									2.698	0.961	0.340
12.0									4.545	1.153	0.408
24.0									7.444	0.993	0.351
36.0									8.979	1.577	0.557
48.0									9.636	2.017	0.713
60.0									10.325	2.347	0.830
72.0									10.586	2.503	0.985
96.0									11.002	2.529	0.894
120.0									11.180	2.518	0.890
144.0									11.237	2.525	0.893

TAB. 21

RENAL EXCRETION OF UNCHANGED SP 54

VOLUNTEER 1,3,5,7 CAPSULE 150 MG
VALUES IN PERCENT OF DOSE/FRACTION

Zeit- Endpunkte	Prob. 01	Prob. 03	Prob. 05	Prob. 07	Mean	SD	SE
0.00					0.0000	0.0000	0.0000
2.00					0.4343	0.2139	0.1070
4.00					0.7995	0.3380	0.1690
12.00					0.9230	0.3401	0.1700
24.00					0.6645	0.8087	0.4044
36.00					0.2607	0.3095	0.1787
48.00					0.0000	0.0000	0.0000

TAB. 22

CUMULATIVE RENAL EXCRETION OF UNCHANGED SP 54

VOLUNTEER 1,3,5,7 CAPSULE 150 MG
VALUES IN PERCENT OF DOSE CUMULATED

Zeit- Endpunkte	Prob. 01	Prob. 03	Prob. 05	Prob. 07	Mean	SD	SE
0.0					0.000	0.000	0.000
2.0					0.434	0.214	0.107
6.0					1.234	0.516	0.258
12.0					2.157	0.705	0.353
24.0					2.821	1.189	0.595
36.0					3.017	1.326	0.663
48.0					3.017	1.326	0.663

Fig. 29:

CUMULATIVE RENAL EXCRETION OF UNCHANGED SP 54 AND TOTAL RADIOACTIVITY

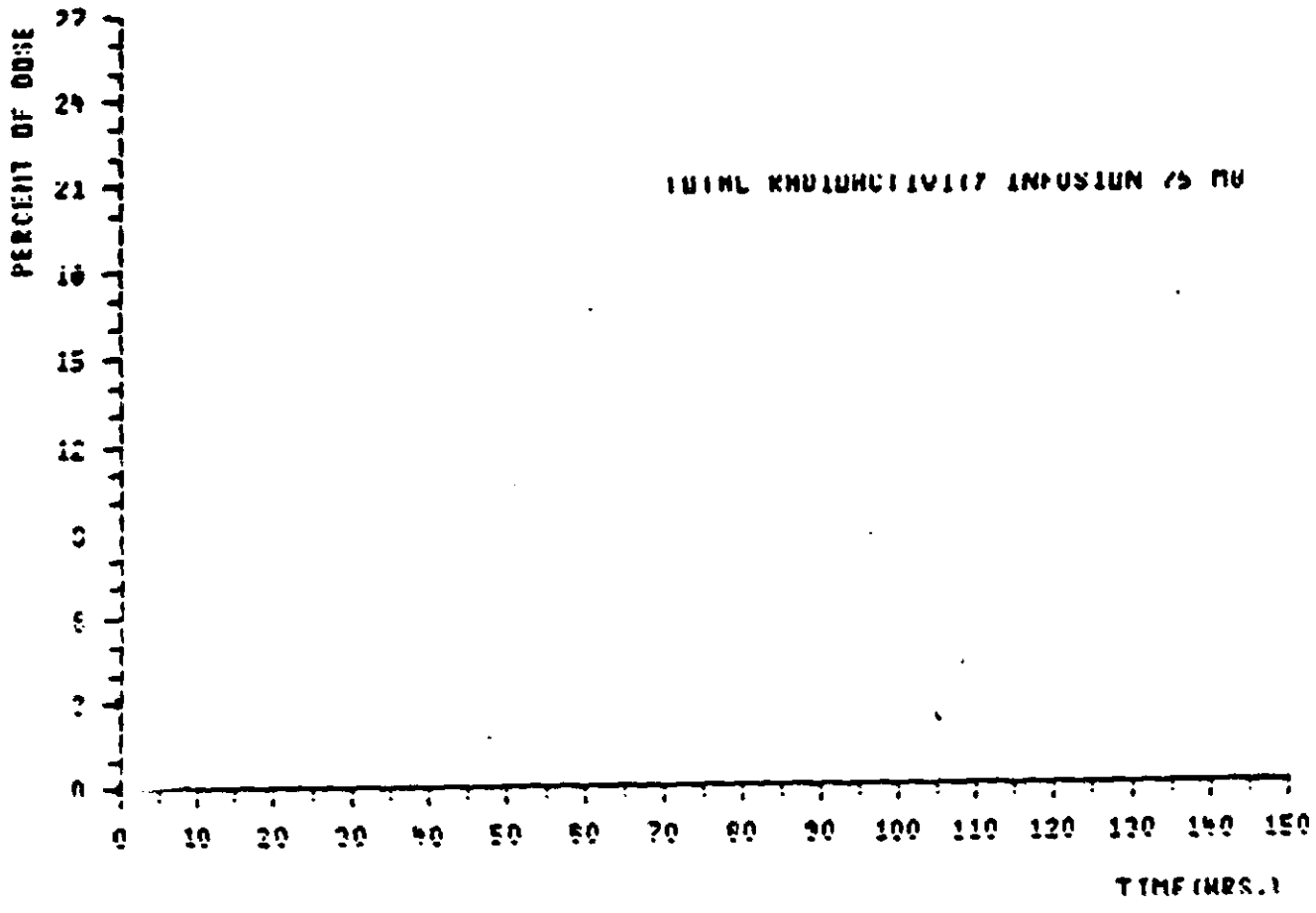
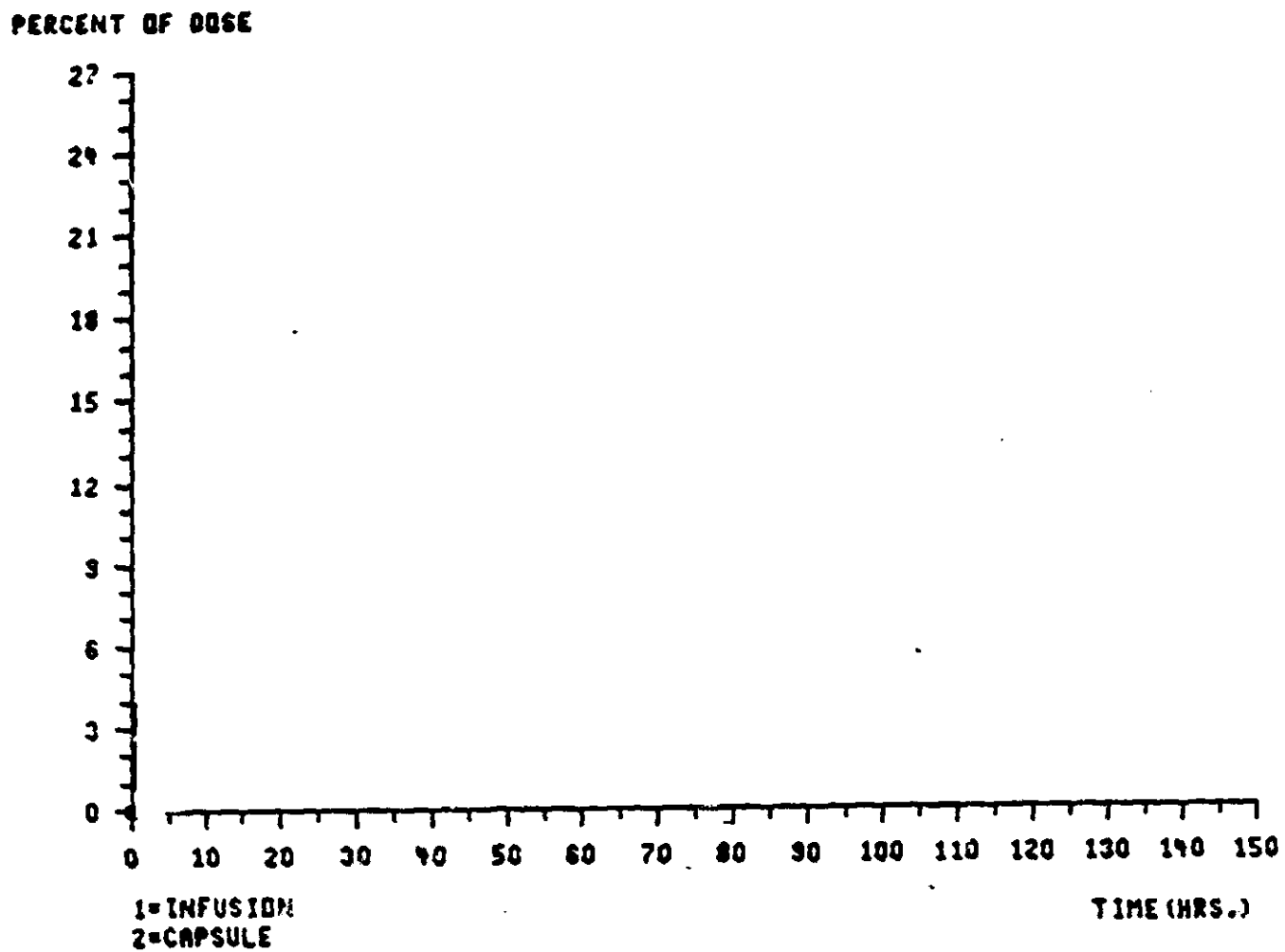


Fig. 28:

CUMULATIVE URINARY EXCRETION OF SP 54 TOTAL RADIOACTIVITY
VOLUNTEER 1-8 (MEAN +/- SEM)



Pharm/Tax

DIV
NDA 20-193

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
Original Summary

NOV 20 1991

Letter Date: 6/11/91
CDER Date: 6/19/91

Reviewer: J.E. Wilson
Review Started: 11/17/91
Review Completed: 12/20/91

APPLICANT: Baker Cummins Pharmaceuticals, Inc.
Miami, Florida

ORGANIZATIONS PERFORMING TOXICITY STUDIES:

FOREIGN ANIMAL STUDIES: Yes

DRUG: ELMIRON® (pentosan polysulfate sodium)

CATEGORY: Anti-inflammatory (interstitial cystitis)

INDICATION: Treatment of interstitial cystitis

CHEMICAL SYNONYM: Sodium xylanpolysulfate

COMPOSITION: Each capsule contains 100 mg of pentosan polysulfate sodium.

RELATED INDS:

DOSAGE: Recommended at 300 mg/day (6 mg/kg) taken as one 100 mg capsule orally three times daily. Maximum permitted dosage was 600 mg/day (12 mg/kg) under related IND

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ACUTE TOXICITY

Species	Strain	No. of Animals per Dose	Route	Observation Period	LD ₅₀ Mg/Kg
Mouse	NMRI	10M/10F	Oral*	14d	>56,200
	NMRI	5M/5F	IM	24h	1,160
	NMRI	5M/5F	IM	14d	893
	NMRI	5M/5F	IV	24h	1,770
	NMRI	5M/5F	IV	14d	1,520
	NMRI	10M/10F	IV	14d	2,740

<u>Species</u>	<u>Strain</u>	<u>No. of Animals per Dose</u>	<u>Route</u>	<u>Observation Period</u>	<u>LD₅₀ Mg/Kg</u>
Rat	Sprague-Dawley	10M	Oral*	14d	49,900
	Sprague-Dawley	10F	Oral*	14d	36,200
	Wistar	5M/5F	IM	24hr	440
	Wistar	5M/5F	IM	14d	308
	Wistar	5M/5F	IV	24h	355
	Wistar	5M/5F	IV	14d	365
	Sprague-Dawley	10M/10F	IV	14d	3,260
	Guinea Pig		5M/5F	IM	24h
		5M/5F	IM	14d	1,230
Rabbit		3M/3F	IM	24h	264
		3M/3F	IM	14d	270

*Three divided doses over a single 24-hr period.

In preliminary experiments by mice experienced intermittent tonic-clonic spasms following 2820 mg/kg intravenously. At 1780 mg/kg intramuscularly, the mouse became quite agitated whenever anyone approached its cage. The rat and guinea pig reacted by displaying hind limb paralysis following intramuscular dosages of 252 and 2000 mg/kg respectively.

Soft feces were observed in all dosage groups in rats after oral administration of the drug. Apathy was another finding in the two highest dosage groups in both rats and mice. Autopsy of both species showed hemorrhagic ascites in rats, hemorrhagic hydrothorax in both species, and congestion of liver and lungs.

Following intravenous injection into the tail vein of the rat and mouse at the two highest dosages (3.56 and 5.01 g/kg), a change in the vascular system of the tail was observed during and immediately after injection. Bleeding took place at the injection site and all visible vessels and tail muscles turned white.

The majority of rats that died following intravenous injection showed hemorrhagic ascites and hydrothorax and congestion of liver and lungs. Mice showed a lower incidence of congestion of lungs with only a few in the high dosage group. Three animals in this same group had congestion of the gastrointestinal tract.

MULTIDOSE TOXICITY STUDIES:

RAT (Shoe: Wist):

Study Number: 18

Test Material: SP 54 (pentosan polysulfate sodium)

No. of Animals/Level: 15M & 15F

Dosage Levels (Mg/Kg): 0, 5, 25, and 100

Duration and Route: 6 Months in the diet plus 3 months recovery period following cessation of medication

Growth: Treated rats paralleled control rats in body weight gain.

Mortality: One control rat accidentally killed during treatment period. Unreported deaths may have occurred in the recovery period.

Hematology: Males receiving 25 and 100 mg/kg developed leukopenia after 5 months that was said to have reversed by the end of the recovery period.

Organ Weights: Females in the 100 mg/kg group had significantly lower mean liver to body weight ratios at the end of the treatment period than their control counterparts.

Gross Pathology: Unremarkable for all groups.

Histopathology: Only the livers and kidneys were examined in the controls and 100 mg/kg groups. Only the livers of the male animals and not the females were examined for fatty changes and no treatment-related effects were noted.

Clinical Behavior: Unaffected by treatment.

RAT (WI-TAR-COX ENTRY):

Study Number: 19

Test Material: CB 8061 (pentosan polysulfate sodium)

No. of Animals/Level: 20 males (treated) 13 males (control)

Dosage Levels:

<u>Group</u>	<u>PPM in Diet</u>	<u>Mg/Kg (Approx.) Initially</u>
A	0	0
B	250	15
C	250	30
D	1000	60

Duration and Route: 52 weeks in diet.

Growth: A statistical comparison was made only between the 60 mg/kg group and the control animals. Mean weight for this last group was significantly lower at 5, 10, and 12 months.

Mortality:

<u>Dosage (Mg/Kg)</u>	<u>% Mortality</u>
0	23
15	30
30	20
60	10

Hematology: The 60 mg/kg group had a significant lower erythrocyte count at 5 months than the control group, but this difference disappeared by the 10th month. Differential monocyte count appears higher than literature values for all groups including controls.

Clinical Chemistry: A comparison is made between the mean values for four rats from the high dosage group and four rats from the control group that had been fasted 24 hours before sacrifice. In a similar manner an analysis for blood and liver was made in four animals from the high dosage group and four animals from the control group that had not been fasted. The parameters included only cholesterol, triglycerides (esterified and non-esterified), mono- and di-triglycerides, and liver glycogen. No trends were apparent from the data presented.

Organ Weights: Mean relative organ weights for heart, lungs, kidneys, spleen, liver, adrenals, seminal vesicles, prostate, testes, hypophysis, epididymal fat, digestive tract, and carcass were given. The values for the high dosage group and the controls paralleled each other. The 30 mg/kg group had a higher mean relative organ weight for the digestive tract than the control group.

Gross Pathology: The investigators state that no gross

abnormalities could be found in the 60 mg/kg and control groups. The investigator did admit, however, to an enlargement of the G.I. tract in the 15 and 30 mg/kg groups.

Histopathology:

Liver.—The 15 and 30 mg/kg groups appeared more affected than the 60 mg/kg and control groups. This was characterized by a certain degree of congestion predominantly in the central lobulus region. There was a lympho-plasmocytic infiltration in the region of the portal vein spaces. One animal in the 30 mg/kg group had an adenoma.

Spleen.—Numerous multinucleated giant cells were observed in the 15 and 30 mg/kg groups but not in the 60 mg/kg and control groups.

Kidney.—No treatment-related anomalies.

Heart.—No treatment-related anomalies.

Thyroid.—Small adenomas were observed in two animals from the 15 mg/kg group and one animal from the 30 mg/kg group.

Intestines.—The investigators state that almost all of the animals that received 15 and 30 mg/kg had significant lesions in their intestinal mucosa that were absent in the controls and 60 mg/kg group. This involved extended areas of mucosal necrosis with ulcerations. More or less organized granulated tissue surrounded the ulcerated zone and necrotic tissue.

An inflammatory reaction extended into the layers of the muscular system. A significant edematous response of the submucosal membrane occurred at the periphery of the ulcerated areas. The lesions were generally confined to the ileocecum.

Investigator's comments.—The intestinal phenomenon was attributed to parasitic origin and enterobacteria. A similar "cage sickness" has been seen in both the investigator's colony and that of the supplier.

RAT (Carworth Farms Europe):

Study Number: 23

Test Material: Graded concentrations of SP 54 (pentosan

polysulfate sodium) in sterile isotonic saline.

No. of Animals/Level: 15M & 15F

Dosage Levels (Mg/Kg): 0, 5, 10, and 25 (increased to 50 after 16 weeks).

Frequency of Administration: 3x/wk.

Duration and Route: 26 weeks subcutaneously. 5M & 5F from each of control, 5 mg/kg, and 10 mg/kg groups were withdrawn from treatment and kept under observation for an additional 13 weeks.

Growth: Males (but not females) showed reduced weight gains between 10 and 16 weeks at 25 mg/kg and further depression at 50 mg/kg. Elevation of dosage from 25 mg/kg to 50 mg/kg in females reversed the slightly greater weight gains than controls to a depression of weight gain and, eventually, to a small weight loss.

Mortality: No treatment-related mortalities occurred until the dosage in the 25 mg/kg group was increased to 50 mg/kg. A total of 14 of 29 rats either died or were killed following the increased dosage.

Food Consumption: During the weeks of treatment, consumption was somewhat increased in all female treatment-groups. After withdrawal of treatment the difference was no longer seen in the 5 mg/kg group.

Clear depression of food intake was evident in males in the 25 mg/kg group at the 17th week when the dosage was elevated to 50 mg/kg.

Hematology: A progressive leucocytosis was observed in both sexes of the 25 mg/kg increased to 50 mg/kg group. This was seen in females in the 10 mg/kg group at termination of treatment but disappeared after treatment was withdrawn. Hemoglobin concentration showed intermittent depression in the 25 mg/kg group. A similar finding was present in the 10 mg/kg group but significance was lost during the 13 week recovery period.

Clinical Chemistry: No indications of treatment-related effects were recorded in the 25 mg/kg (increased to 50 mg/kg) group until the 24th week. Findings at that time included depressed blood glucose concentrations, mildly elevated alkaline phosphatase activity, plus a similar elevation of serum potassium. At 26 weeks, the 10 mg/kg group had similar changes in the blood chemis-

try with the exception that serum alkaline phosphatase was unaffected. The changes in the 10 mg/kg group persisted through the 13-week withdrawal period.

Urinalysis: Unaffected by treatment.

Organ Weights: Mean relative weights for both the liver and spleen were statistically increased in all treated males at 26 weeks when compared with their control counterparts. The same was true for treated females but only in the 10 and 25-50 mg/kg groups. Other organs whose mean relative weight was increased in the 10 and 25-50 mg/kg groups included the kidneys, thyroid, and pituitary. Females in the 25-50 mg/kg group had increased heart weights.

Both males and females had significantly increased mean relative weights for liver in the 10 mg/kg group even after a 13-week withdrawal period. Only females in this same group had increased relative kidney weights.

Gross Pathology:

Injection site.—A small nodular thickening and a minimal degree of hair loss were present in the 5 mg/kg group. These changes tended to be more pronounced in the 10 mg/kg group, while in the 25-50 mg/kg group scab formation or ulceration with secondary infection was seen in many animals.

Spleen.—Enlargement was present in the 25-50 mg/kg group.

Liver.—The 5 mg/kg group had a granular surface due to heightening of the normal lobular pattern. This appearance was repeated in 10 mg/kg and 25-50 groups where lobular swelling was apparent. A pale coloration to a gray color was present in the high dosage group.

Pancreas.—Some 25-50 mg/kg animals had a gelatinous appearing pancreas suggestive of a degenerative change.

Stomach.—Petechial hemorrhages were noted in the gastric mucosa of three 25-50 mg/kg animals.

Histopathology:

Liver.—Severe fatty changes were present throughout male and female rats in the high dosage group. A minimal degree of bile duct proliferation was present in most rats in this group. Females in the 10 mg/kg

group had severe fatty changes that were present throughout the liver lobules, whereas, in males, the changes tended to be localized to groups of hepatocytes irregularly distributed throughout liver lobules. In the 5 mg/kg group, 5 females and 5 males showed fatty changes involving groups of hepatocytes or complete lobules, and in 5 female rats a minimal degree of bile duct proliferation was present.

10 mg/kg and some 5 mg/kg rats had a few enlarged hepatocytes with marked cytoplasmic vacuolation, indicative of fatty changes following the 13-week withdrawal period. The change was much less marked than in rats killed at the conclusion of the 26-week treatment period. A progressive increase in minimal bile duct proliferation was still present at the end of the withdrawal period.

Kidney.—Degeneration and vacuolation were seen in the epithelium of many proximal convoluted tubules in male and female rats of the high dosage group. The epithelium of many proximal convoluted tubules in male and female rats of the 10 mg/kg group, and in females of the 5 mg/kg group had a granular appearance and contained microvacuoles.

Spleen.—Numerous macrophages, often with vacuolated cytoplasm, were present in the red pulp of the high dosage group. Similarly, macrophages were present in the spleens of 10 mg/kg group and in one 5 mg/kg rat, but were much less evident.

At the conclusion of the withdrawal period, a few macrophages with partially vacuolated cytoplasm were seen in some 10 mg/kg rats. The numbers were fewer than when the rats were killed at the end of the treatment period.

Lymph nodes.—Numerous macrophages, often with vacuolated cytoplasm, were present within the medulla of lymph nodes from the high dosage group, the 10 mg/kg animals, and some from the 5 mg/kg group. The number of macrophages were much fewer in animals allowed to recover from treatment than in those animals sacrificed at the end of treatment.

Skin.—Animals receiving 5 and 10 mg/kg had a moderate fibroblastic response usually present in the subcutaneous tissue and sometimes associated with hemorrhage at the injection site. Animals in the 25-50 mg/kg group often showed marked fibroblastic response with

loss of epidermis.

Atrophy of hair follicles was seen in male and female rats in the 5 and 10 mg/kg groups at the end of the recovery period. An epidermal ulceration was present in some 5 mg/kg rats and was associated with a minimal to moderate degree of subcutaneous fibrosis.

Other Comments: A local reaction at each injection site eventually included minimal hair loss and thickening of the skin in the 5 mg/kg group, extending with greater severity in the 25-50 mg/kg group. Areas of frank alopecia and subcutaneous hemorrhage were noted in this last group.

Monkey (Macaca mulatta):

Study Number: 25 (Dated 1972)

Test Material: Solid Compound SP 54 (pentosan polysulfate sodium) was dissolved in distilled water.

Protocol:

<u>Group</u>	<u>No. of Animals</u>		<u>Daily Dose</u>
	<u>Male</u>	<u>Female</u>	<u>Level</u> <u>Mg/Kg</u>
Control	3	3	0
Low	2	2	2
Medium	2	2	50
High	2	2	200

Duration and Route: Daily oral gavage for six months

Growth: Body weight gain was significantly depressed below control rates during the latter half of the dosing period among the high dose animals leading to marked body weight losses that amounted to 30 to 40 % when compared to controls. Males in the 50 mg/kg group showed decreases in weight gain in the first half of the dosing period and then later they paralleled the control group.

Mortality: Two males and one female in the 200 mg/kg group died during the fifth month.

Food Consumption: Significantly reduced in the 200 mg/kg group after three months of dosing. Food intake was normal in the other test groups.

Hematology: Males in the 200 mg/kg group experienced an

anemia plus leukocytosis with a high differential neutrophil shift by the fourth month. The effect was less pronounced in females in this group with the differential neutrophil shift only slightly above control values.

Clinical Chemistry: Males in the 200 mg/kg group had moderately increased BUN values and decreased serum alkaline phosphatase levels by the fourth month. Females in this same group did not have the increase in BUN but did experience a decrease in serum alkaline phosphatase. No differential biochemical effects were detected at the two lower dosage levels.

Urinalysis: Significant but small amounts of protein and blood cells were found in the urine of the 200 mg/kg females at four months, whereas significant small amounts of blood cells but moderate amounts of protein were found in the urine of the males in this same dosage group and time period.

Fecal Examination: Occult blood was regularly present in monkeys in the 200 mg/kg group and was roughly proportional to the degree of diarrhea. A trace amount of blood was present in 1 of 2 males at four months only and 1 of 2 females after six months in the 50 mg/kg group.

Gross Pathology: Abnormalities found in the three animals in the 200 mg/kg group that died before the end of the treatment period were restricted principally to considerable quantities of blood in the lumen of the small and large intestines (and, additionally, in the stomach of one of the animals). No grossly hemorrhagic foci could be visualized on careful examination of the entire gastrointestinal tract. The liver of the animal that had blood in its stomach had a granular texture and the gall bladder was distended. No gross abnormalities were found in the control, 2, and 50 mg/kg groups.

Histopathology:

2 Mg/kg group.—1 of 2 males had a simple reactive hyperplasia of the lymph node. Both females had either a possible increase in mucosal capillaries or inflammation and edema of the villous structure of the ileum. The colon of these same females had mucosal capillaries that were prominent and congested in the sub-mucosa.

All other tissues were normal.

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50 Mg/kg group.—The ileum of one male had congested capillaries in the mucosa and sub-mucosa without inflammation. The mesenteric vessel in this same animal showed marked congestion. The ileum of the second male had moderate sub-capillary dilatation with small capillaries prominent in the lamina propria (connective tissue just below the epithelium and basement membrane). Evidence of hemorrhage was not present in this animal.

The two females in this group had either mild or moderate vascular congestion of the sub-mucosa of the colon. The ileum of one female had a mild sub-mucosal congestion.

All other tissues were normal.

200 Mg/kg.—The colon of one of the two surviving males had mild to moderate congestion of the sub-mucosa with prominent capillaries in the lamina propria. The colon of the second male had lymphoid hyperplasia. This last male also had mild capillary dilatation of the sub-mucosa of the ileum.

One of two surviving females in the 200 mg/kg group had the ileum, colon, and a lymph node affected by treatment. The ileum had mild to moderate capillary dilatation in submucosa and dilated capillaries in lamina propria. The colon had mild capillary dilatation in lamina propria and the lymph node had reactive hyperplasia. The second surviving female had only dilated mucosal and submucosal capillaries of the ileum.

All other tissues were normal.

Behavior: One moribund male for a full day preceding death in the 200 mg/kg group had blood grossly visible about the mouth and anus as well as in the diarrhetic feces. No abnormal behavior was noted in the 2 and 50 mg/kg dosage groups.

OTHER MULTIDOSE TOXICITY STUDIES:

Rat (Wistar):

Study Number: 20

Test Material: SP 54 (pentosan polysulfate sodium)

No. of Animals/Level: 10 M & 10 F

Dosage Levels (Mg/Kg): 0, 5, 15, and 25

Duration and Route: Intraperitoneal for 3 weeks plus a 3-week recovery period.

Growth: Surviving male rats in the 5 and 25 mg/kg groups exceeded the control group in weight gain, whereas the remaining males and surviving females paralleled the control group.

Mortality: 2 of 10 males and 1 of 10 females in the 25 mg/kg group.

Food Consumption. Treated groups paralleled control.

Hematology: Only 3 males and 3 females from each group were examined. One male had a high differential eosinophil count at the end of the recovery period.

Clinical Chemistry: Cholesterol was reduced at the end of the treatment period in the 15 and 25 mg/kg groups that returned to normal at the end of the recovery period.

Organ Weights: Increased relative liver weight in females in the 15 mg/kg group and in both males and females in the 25 mg/kg group when compared to control animals. Relative kidney weights were unaffected by treatment.

Gross Pathology: Fatty changes in the livers of both sexes in the 25 mg/kg group.

Observations: No abnormal reactions were noted.

RAT (Charles River CD):

Study Number: 22

Test Material: Stock solution containing 100 mg/ml of sodium pentosan polysulfate in sterile saline was diluted with Sodium Chloride Injection prior to injection.

No. of Animals/Level : 25M & 25F

Dosage Levels (Mg/Kg/Day): 0, 5, 10, and 20.

Duration and Route: Subcutaneously on the dorsal surface of the back seven days a week for four weeks. Ten surviving males and ten females in each group were sacrificed after four weeks of treatment. Remaining rats received no further treatment from that time until sacrifice after a recovery period of nine weeks.

Growth: Treated groups paralleled control group.

Mortality: All animals survived treatment period. Two rats that had received 5 mg/kg/day died at blood sampling during recovery period. Another male receiving 5 mg/kg/day was found dead in the recovery period following weight loss. One high dose female was found dead in recovery period and necropsy revealed subcutaneous hemorrhage at injection sites and hydronephrosis.

Food Consumption: Food intake of treated rats was similar to that of the controls during treatment period.

Females that received treatment consumed more food during the recovery phase than did control females.

Hematology: Dose related declines that were marginal were observed in all treated groups in comparison with the controls after three weeks of treatment. Statistical significance was achieved only in the case of males receiving 20 mg/kg/day. Higher leukocyte counts were recorded in males and females receiving 20 mg/kg/day and this was associated with an increase in the proportion of neutrophils.

Coagulation Tests: Values for prothrombin time were higher than those of controls in males and females receiving 20 mg/kg/day and in females receiving 10 mg/kg/day. Activated partial thromboplastin times of rats receiving 20 mg/kg/day were slightly elevated, but bleeding times were unaffected.

Clinical Chemistry: After three weeks the plasma protein concentrations were lower than the respective controls. There was no dose effect relationship and the effect was most pronounced in females. After four weeks of recovery these differences were no longer apparent.

Urinalysis: Unaffected by treatment.

Organ Weights: Females from all treated groups had high mean relative liver and kidney weights than their control counterparts. The effect was dose-related and the differences were significant. Males and females had significantly higher mean relative spleen weights in the 20 mg/kg/day dosage group.

After a recovery period of 9 weeks mean relative liver weight for all treated groups was significantly higher than control values. Mean relative adrenal weights in the high dose males and the 10 and 20 mg/kg/day females

were high compared with their respective controls.

Gross Pathology: The effects seen at the injection site were more pronounced in the 20 mg/kg/day group and possibly the 10 mg/kg/day group and included subcutaneous hemorrhage, edema, subcutaneous hematoma, foci of necrosis, and focal surface encrustation with small abscesses.

Following the recovery period, a number of discrete subcutaneous hematomas were still present in those rats that had received 10 or 20 mg/kg/day.

Histopathology:

A.—Microscopic examination of animals killed at the end of the treatment period revealed the following changes which were considered to be related to treatment:

At 20 mg/kg/day:

Extensive changes in the injection sites characterized by hemorrhage, necrosis, edema and chronic inflammatory cell infiltration in which fibroblasts and macrophages predominated.

Apparent fatty changes in the livers of both males and females.

The presence of vacuolated cells in the tubules of the outer cortex of the kidneys in a proportion of both males and females.

The presence of foam cells in the lymph nodes of most animals and in the spleen of one.

At 10 mg/kg/day:

Moderate changes at the injection sites characterized by hemorrhage, edema and inflammatory cell infiltration in which fibroblasts and macrophages predominated.

Moderate fatty changes in the livers of a proportion of males and females.

The presence of foam cells in the lymph nodes of most animals.

At 5 mg/kg/day:

Moderate changes at the injection sites characterized

by hemorrhage, and edema associated with moderate chronic inflammatory cell infiltration in which fibroblasts and macrophages predominated.

The presence of foam cells in the mesenteric lymph nodes of most animals.

E.—In animals killed after the recovery period, as compared with the animals killed immediately after completion of the treatment period, microscopy revealed:

At 20 mg/kg/day:

A reduced level of inflammatory change at the injection sites associated with hemorrhages, showing evidence of regression in many animals.

A reduced level of vacuolation in the livers of both males and females.

A reduction both in the incidence and extent of foam cells in the lymph nodes.

At 10 mg/kg/day:

A reduction in the changes seen at the injection sites, such that in only a few animals was there a moderate degree of fibrosis seen to be associated with hemorrhages which were showing evidence of regression.

Only one animal showed a degree of vacuolation in the liver that could be considered to be related to the change seen at termination.

A reduction in the incidence and extent of foam cells in the lymph nodes.

At 5 mg/kg/day:

Regression of inflammatory changes at the injection sites such that only minimal fibrosis was seen in three instances.

A reduction in the incidence and extent of foam cells in the mesenteric lymph nodes, although these were still present to a minimal or moderate degree in approximately half the animals.

Observations: Visible reactions to treatment were confined to the injection sites and consisted of localized bruising and swelling, followed by hemorrhage, crusting, and

necrosis. These signs regressed during the recovery period.

RAT (Wistar):

Study Number: 21

Test Material: SP 54 (pentosan polysulfate sodium) in a 10% aqueous solution was diluted 1:15 with 0.9% NaCl solution, and later, when the rats weighed more than 200 g, the dilution was 1:10.

No. of Animals/Level: 6M & 6F in treated groups and 10M & 10F in control group.

Dosage Levels (Mg/Kg/Day): 0, 5, 10, and 20

Frequency of Administration: 3x/wk

Duration and Route: 14 weeks subcutaneously.

Volume of Injection: 0.12 mL for 5 mg/kg when rats weighed 150 g to 0.7 ml for 20 mg/kg when rats weighed 350 g.

Growth: Treated animals paralleled control group.

Mortality: 1 of 20 control animals. No animals died in the treated groups.

Food Consumption: Unaffected by treatment.

Hematology: Leukocyte counts were without exception low. Most values were in the lower range of the investigator's standard values. Treatment had no influence on leukocyte counts.

Clinical Chemistry: SGPT, blood glucose, total cholesterol, and serum urea were unaffected by treatment.

Urinalysis: Unaffected by treatment.

Organ Weights: Mean relative weight for liver for the treated females was significantly higher than their control counterparts. Only in the males of the highest dosage group was the mean relative weight of the liver significantly higher than in the controls. Only at 20 mg/kg was the mean relative weight for the kidneys significantly elevated.

Histopathology: The most striking finding was the hepatic swelling that was seen only in treated animals. This

was associated by the disappearance of the radial striping in the hepatic lobules.

At 5 mg/kg only hepatic swelling and isolated vacuoles were noticed.

At 10 mg/kg individual liver cells were stated to have hepatic swelling, vacuoles, and degenerative manifestation without the exact frequency being stated. The presence of dark cells, often containing two nuclei, appear to imply that individual hepatic cells were irreversibly damaged and replaced by regeneration. No nuclear alterations (karyorrhexis or pyknosis) occurred.

At 20 mg/kg, hepatic swelling was also present with vacuoles approximately the same number and size as in the 10 mg/kg group. Individual cellular nuclei were pyknotic with signs of regeneration very rarely seen (much less than in the 10 mg/kg group).

Although the liver vacuoles had a close resemblance to fatty vacuoles, the histochemical preparation was shown to be almost fat free.

When liver was stained with toluidine blue, the pento-sanpolysulfuric acid ester of the dye could be demonstrated to be present metachromatically. The mast cells occurring subcapsularly and in the connective tissue were dark blue-violet in color.

Rats in both the 10 mg/kg and the 20 mg/kg groups had low grade swelling of the kidneys in isolated areas. These same groups had isolated small vacuoles in the renal tubular epithelium.

Other Comments: All animals were in good or exceptionally good nutritional condition.

RABBIT (New Zealand White):

Study Number: 24

Test Material: Graded solutions of SP 54 (pentosan polysulfate sodium) in isotonic saline.

Protocol:

GROUP	Dosage (MG/KG)	No. of Rabbits	
		M	F
1	0		
2	2	6	6
3	5	5	5
4	10	5	5
5	15	5	5
		6	6

Volume/Dose: 0.25 mL/kg including saline for control animals.

Duration and Route: Daily subcutaneous injections, seven days a week, for a total of five weeks. Three males and three females from each of Groups 1 and 5 at the end of the treatment period were held without further treatment for an additional ten weeks before sacrifice.

Growth: Rabbits in the 15 mg/kg dosage group experienced a mean weight gain that was less, but not more than a 10% loss, when compared with the control group.

Mortality: One male and one female in the 15 mg/kg group.

Food Consumption: Progressive depression in the female in the 15 mg/kg group that died and anorexia with subsequent death in the male in the same group.

Hematology: Hematocrit, hemoglobin concentration, and cellular counts were unaffected by treatment.

Clinical Chemistry: Plasma urea, blood glucose, serum alkaline phosphate, SGPT, blood electrolytes, and serum protein were unaffected by treatment.

Urinalysis: No treatment-related differences between treated and control groups were noted.

Organ Weights: In males, relative spleen weights showed some tendency to increase with relation to treatment, but there was no supporting evidence in females.

Mean relative organ weights for the liver reached a maximum in the 10 mg/kg group, but a lower value was attained in the 15 mg/kg group. Only three animals per sex were sacrificed in each of the control and 15 mg/kg groups and this renders an association with treatment tenuous.

Gross Pathology: Slight hemorrhage at the injection site

was found in 4 of 54 treated animals which did not appear to be dose related.

Histopathology:

After 5 weeks of treatment.—Treatment-related changes were confined to the kidney where cytoplasmic vacuolation of the epithelium of proximal convoluted tubules was observed in the high dosage (15 mg/kg) animals. Rabbits in the 5 and 10 mg/kg groups had a granular appearance of the renal tubular cytoplasm. The investigators considered this as a storage phenomenon.

Metachromasia (the same stain produces different tints in different tissues) was seen in the cells of the hepatic reticulo-endothelial system in the 5, 10, and 15 mg/kg dosage groups, and in some animals in the 2 mg/kg group.

10 Weeks After withdrawal from treatment.—Metachromasia was seen in the livers of all rabbits in the 15 mg/kg group, but the amount of positive material was marginally less than that seen in animals of the comparable group sacrificed immediately after five weeks of drug administration.

Either a few basophilic casts within the medulla or a few atrophic tubules with some exhibiting marked cytoplasmic vacuolation were seen in 4 of 5 rabbits in the 15 mg/kg group. No fat was observed when stained with Oil Red O.

Clinical Observations: No signs of general toxicity or abnormal behavior were seen with the exception of softening of the feces in the 15 mg/kg group and sporadically in a few other treated animals.

BABOON:

Study Number: 27

Test Material: SP 54 Ampules containing 100 mg of pento-
san polysulfate sodium in 1 mL fluid. Further dilution
with isotonic saline was made in order to provide a
constant volume-dosage of 1 ml/kg.

Protocol:

Group	Dosage (Mg/Kg/Day)	No. of Animals			
		Treatment		Recovery	
		M	F	M	F
1	Control	5	5	2	2
2	4.5	3	3	-	-
3	6.7	5	5	2	2
4	10.0	5	5	2	2
5*	10.0	1	1	-	-
6*	15.0	1	1	-	-

*Separate study reported May 3, 1979.

Duration and Route: Subcutaneous injections daily for seven days a week for four weeks. Five-week recovery period.

Growth: Body weight loss was recorded during the treatment period for most males and females receiving 10 mg/kg. The losses were particularly severe from Day 12 of treatment onwards in monkeys treated with 15 mg/kg/day.

Mortality: Both animals in the 15 mg/kg/day group were killed in extremis during the the third week of treatment. 1 of 8 baboons (female) receiving 10 mg/kg/day was killed in extremis during the fourth week of treatment.

Food consumption: Several animals receiving 10 mg/kg/day exhibited a tendency towards reduced food intake. This trend became more evident during the second half of the study. Over the final days of treatment food consumption was markedly reduced in both animals receiving 15 mg/kg/day.

During recovery period those animals previously treated with the drug had food consumption similar to that of the controls.

Hematology: The one male receiving 15 mg/kg/day had a low total white corpuscular count when examined before being killed in extremis.

Coagulation Tests: All animals in the 10 and 15 mg/kg/day groups had marked elevation of the partial thromboplastin time. One male and several females receiving 6.7 mg/kg/day manifested a similar response to treatment when compared with their pretreatment values.

Those animals in the study reported in 1979 plus one female in a later study receiving 10 mg/kg had increases in prothrombin time.

Bleeding times and platelet counts were unaffected by treatment.

Clinical Chemistry: Assessment of inter-group differences was made difficult because of wide variations in individual values.

Increased plasma urea, potassium, or calcium concentrations were noted by the investigators after three weeks of treatment among some animals receiving 6.7 or 10.0 mg/kg/day. These effects did not persist during the recovery period.

The female dying in extremis at 15 mg/kg had a severely increased serum glucose concentration that may have contributed to this animal's debility. A slightly reduced sodium value was found in this same animal.

Urinalysis: A strong reaction for acetone was observed in 2 of 4 females and 1 of 5 males after three weeks of treatment in the 10 mg/kg/day group in the main study. Further, the female in the 10 mg/kg/day group (not included above) that died during treatment had a positive ketone reaction. A moderate reaction was also observed in a control male three weeks after the commencement of treatment. A minimal degree of contamination due to a small sample may have occurred in this last animal.

The positive ketone reaction in the two surviving and the one sacrificed females in the 10 mg/kg group was accompanied by a lowered urinary pH.

Ophthalmoscopy: Unaffected by treatment.

Electrocardiography: Unaffected by treatment.

Organ Weights: Increased significant relative weight of the adrenals was revealed when animals receiving 10 mg/kg/day were killed after four weeks of treatment. However, the difference was not significant when the animals were allowed to recover. Relative kidney weights were higher for the two animals treated at 10 mg/kg/day than is usually found in baboons, but this may have been a reflection of the marked weight loss.

Gross Pathology: Necropsy after four weeks of treatment revealed subcutaneous hemorrhage, edema, and tissue thickening at the injection sites of most treated but not control animals. Darkened coloration and/or congestion of the adrenal glands was observed in several animals receiving 4.5 or 6.7 mg/kg/day and in all

baboons treated at 10 mg/kg/day.

Injection site changes were still apparent in treated animals sacrificed after five weeks of recovery, but these were less severe than those seen in animals killed after the treatment period.

Congestion or hemorrhage of the mucosa of the colon occurred in both animals treated with 15 mg/kg/day. This was attributed to scouring caused by diarrhea.

Histopathology: Subcutaneous chronic inflammation and hemorrhage were present at the injection sites of most treated animals plus acanthosis in some animals receiving 6.7 or 10 mg/kg/day. Further treatment-related distributions included pallor of the adrenal cortex at all three dosage levels in the main study and perifollicular cell hyperplasia in the thyroids of some animals receiving 6.7 or 10 mg/kg/day.

Other Comments: Animals receiving 15 mg/kg/day deteriorated rapidly over the three days before sacrifice. Loss of appetite, weight loss, subdued mood, and diarrhea were observed.

Signs at the injection sites were generally clearly evident 24 hours after administration, but in the 15 mg/kg/day group, they were seen only rarely 7 days after dosing.

The incidence of scab formation at the injection sites was increased in animals receiving 6.7 or 10 mg/kg/day and the incidence, severity, and persistence of localized swelling at the injection sites was also increased in these animals. Swelling persisted during the recovery period in several of these animals for up to three weeks.

A number of treated animals became subdued, particularly during the final week of treatment, and this was often accompanied by a loss of balance. This effect was seen in one animal during the first two weeks of recovery. These signs were usually associated with a severe reaction at one or more injection sites and were attributed to involvement of the back muscles in the local reaction to the injection rather than to a central effect.

MONKEY (Macaca rhesus):

Study Number: 26

Test Material: SP 54 (pentosan polysulfate sodium) was available as a 10% solution in 1 mL original vials. For injection, one solution was diluted with isotonic saline to 5%. Control animals received 0.3 mL isotonic solution per kg.

No. of Animals/Level: 1M & 2F

Dosage Levels (Mg/Kg): 0, 10, and 20

Duration and Route: Daily intramuscularly for 21 days. All animals were allowed to recover for three weeks following termination of medication.

Growth: Two surviving control animals showed regular weight gain after the adaptation period. The surviving male in the 10 mg/kg group weighed more at the end of the recovery period than during the pretreatment period. This last animal's weight gain occurred during the recovery period and after the cessation of medication.

The animals treated with 20 mg/kg lost weight persistently even after treatment was stopped.

Mortality: One control male and one 20 mg/kg female died during the recovery period. Another 10 mg/kg female died during the second week of drug treatment.

Hematology: With the exception of one 10 mg/kg female all animals had lowered hemoglobin concentrations at the conclusion of drug treatment than prior to treatment. Those animals in the 20 mg/kg group continued to lose hemoglobin during the recovery period.

The leukocyte count showed a tendency towards decline in all groups including controls. One exception was a male in the 10 mg/kg group that had a distinct rise in leucocyte count during the recovery period. Differential counts were deemed to be in the normal range, but wide variances were noted in the treated group.

Clinical Chemistry: Those animals in the 20 mg/kg group had serum total protein concentrations that were in the lower range of normal values and values that continued at the lower limit or below during the recovery period.

No definitive trends could be established in the values for serum urea and SGPT.

Gross Pathology: One animal in the 20 mg/kg group at the end of the recovery period had intestines with a moder-

ate amount of watery fluid. The mucosa of the small intestine was covered with a grey matter that would partly come off, and in some places the mucosa was very red. Another animal sacrificed at the end of the recovery period had contents of the stomach and intestines that were watery and mucous. A third animal in the 20 mg/kg group dying in the second week of the recovery period had slightly red mucosa of the colon that was covered with obscure mucous. A catarrhal to purulent-necrotizing enteritis was seen in all animals except 2 of 3 control animals.

Histopathology: Hepatic vacuoles were absent in all control animals, but in the treated animals they occurred predominantly in the center of the lobules. In the 20 mg/kg group the vacuoles were more prominent and spread over a larger area of the liver. In this last group, the vacuoles extended more often to the periphery of the hepatic lobules. Nuclear alterations appeared more frequently in the 20 mg/kg group, but they were still rare.

Other Comments: Of the three animals dying before completion, one 10 mg/kg animal had severe enteritis and two other animals (one control and one 20 mg/kg) had a severe form of organic tuberculosis.

BABOON:

Study Number: 28

Test Material: SP 54 Ampules containing either 4 mg/mL, 10 mg/mL, or 20 mg/mL of pentosan polysulfate sodium colorless liquid.

Protocol:

<u>Group</u>	<u>Dosage (Mg/Kg)</u>	<u>Number of Animals</u>	
1	10-15*	M 4	F 4
2	5	2	2
3	2	2	2
4	Controls	2	2

*10 mg/kg raised to 15 mg/kg after 6 weeks.

Duration and Route: Subcutaneous injections three times a week for 13 weeks. 2M & 2F in the high dosage group were observed for a further eight weeks following termination of dosing.

Volume of Injection: 0.5 mL/kg except when high dosage was changed and then the volume became 0.75 mL/kg.

Growth: Suppression of body weight was observed at highest dosage level of 15 mg/kg.

Mortality: 2 of 8 baboons receiving 15 mg/kg died within a week after cessation of dosing.

Food Consumption: Over the last half of the dosing period, three animals receiving 15 mg/kg showed a marked reduction in food intake.

Hematology: Hemoglobin concentration, red cell, white cell, and platelet counts were unaffected by treatment.

Coagulation Tests: Males, in particular in the 10-15 mg/kg dosage group, had prolonged prothrombin times. Mean value for all animals in this group was significantly increased over that of the control group.

Whole blood clotting times were unchanged for the first eight weeks of dosing, but preterminal values for one male in the 15 mg/kg group showed a statistically significant increase over that of the control animals.

Three baboons in the 15 mg/kg group that were allowed to recover from dosing showed a return to normal values within four weeks for prothrombin time and whole blood clotting time.

Clinical Chemistry: Two animals in the high dosage group had elevated plasma urea levels at the end of 12 weeks. One animal died within a few days and the other one within a week. Equally high values were seen in 2 of 4 control animals at the termination of the dosing period.

Urinalysis: Unaffected by treatment.

Ophthalmoscopy: No evidence of toxic damage to the eyes was observed at any time.

Organ Weights: The mean relative weight for livers in the high dosage group was significantly higher than that for the controls. Mean values for the 2 and 5 mg/kg group were higher than controls but statistical significance is unknown.

Three animals in the 15 mg/kg group were observed for 8 weeks after cessation of dosing; Baboon 137 had a very

heavy liver while the remaining two animals had liver weights that were less than the liver weights measured immediately after cessation of dosing in the animals from the same group.

Gross Pathology: None of the anomalies were associated with drug administration.

Histopathology: Toluidine blue positive material was deposited in the liver in greater quantities in the 5 and 10-15 mg/kg groups than in the 2 mg/kg and control groups. This material tended to persist in the reticulo-endothelial cells over the subsequent observation period of eight weeks.

The livers of all animals including controls were stained with Oil Red O and a minimal amount of fat was seen in some hepatocytes of two animals, a high dose male that was observed for 2 months after cessation of dosing and one male in the control group. All other animals had no hepatic fat deposits.

11 of 16 treated animals had a variable degree of atrophy of the cervical and/or mesenteric lymph nodes. None of the control animals were affected in this manner.

8 of 16 treated and 1 of 4 control animals had an enlargement of cells within the zona fasciculata of the adrenal gland.

The majority of treated animals showed a moderate fibroblastic response in the subcutaneous tissue at the injection site associated with hemorrhage and/or cellular infiltration.

Other Comments: Following the increase in high dose level to 15 mg/kg, there was a decline in general health condition associated with lethargy. Slight hardening of the skin locally at the injection site was observed in the high-dose level animals but without any definite evidence of local irritation.

GUINEA PIG SENSITIZATION STUDY

Study Number: 30 (Dated 1989 and conforms to GLP)

Test Material: Solid pentosan polysulfate sodium. Subsequent pastes were made with distilled water at suspensions of 1000 and 100 mg/mL.

No. of Animals: 10 young adult males

Procedure: The method follow was that of Buehler (reference not given).

Induction.—For the first induction, a paste consisting of 0.5 g of the powdered test article and 0.5 mL of distilled water was applied topically under an occlusive patch and exposure was maintained for six hours. A week later a second application was made using 50 mg mixed with 0.5 mL of water, and a third application was made using this last mixture at still another week later. Each induction site was examined and scored for erythema and edema according to the Draize method.

Challenge.—After a two-week rest period, the animals were challenged with the test article (50 mg mixed with 0.5 mL of distilled water) at both the treated site (right side) and a virgin site on the left side. The test article remained in contact with the skin for six hours and the reactions scored at 24 and 48 hours post application.

Results: The test article caused a very slight erythema (Grade 1) in 70% of the guinea pigs with the degree of irritation the same after induction as after challenge. The redness was apparent at 24 hours after application and by 48 hours it usually was still present. The size of the reddened area, when present, was always similar following induction and challenge.

None of the ten guinea pigs challenged had a substantially higher irritatic score than in the induction period. By contrast, guinea pigs treated with p-phenylenediamine all had substantially higher scores after challenge than after induction.

Conclusion: Pentosan polysulfate sodium was not considered a sensitizer in guinea pigs.

ADME—PHARMACOKINETIC STUDIES:

1. Comparison of the retention of pentosan polysulfate sodium and heparin in rat tissues :

Study Number: 29

Test Materials: SP 54 (pentosan polysulfate sodium) and heparin were dissolved in separate solutions of isotonic saline.

Protocol:

<u>Group & Dosage</u>	<u>Route</u>	<u>Post-mortem</u>	<u>No. of Rats</u>	
			M	F
A-1 Heparin 50 mg/kg	i.v.	1st day after injection	3	3
A-2 Heparin 50 mg/kg	i.v.	7th day after injection	3	3
A-3 Heparin 50 mg/kg	i.v.	21st day after injection	3	3
A-4 Control	i.v.	21st day after injection	3	3
A-5 SP 54 50 mg/kg	i.v.	1st day after injection	3	3
A-6 SP 54 50 mg/kg	i.v.	7th day after injection	3	3
A-7 SP 54 50 mg/kg	i.v.	21st day after injection	3	3
A-8 Control	i.v.	21st day after injection	3	3

<u>Group & Dosage</u>	<u>Route</u>	<u>Post-mortem</u>	<u>No. of Rats</u>	
			M	F
B-1 Heparin 10 mg/kg	s.c.	7th day after injection	3	3
B-2 Heparin 10 mg/kg	s.c.	14th day after injection	3	3
B-3 Heparin 10 mg/kg	s.c.	28th day after injection	3	3
B-4 Control	s.c.	28th day after injection	3	3
B-5 SP 54 10 mg/kg	s.c.	7th day after injection	3	3
B-6 SP 54 10 mg/kg	s.c.	14th day after injection	3	3
B-7 SP 54 10 mg/kg	s.c.	28th day after injection	3	3
B-8 Control	s.c.	28th day after injection	3	3

Duration: Single injection by the intravenous route (Part A) and daily by the subcutaneous route for eight days (Part B).

Volume of Injection: 1 mL/kg intravenously and 5 mL/kg subcutaneously.

Gross Pathology:

Kidney.—Bilateral pallor was noted 7 days after the last injection in 5 of 18 rats injected subcutaneously with 10 mg/kg of pentosan polysulfate sodium. 1 of 18 rats had pale dark subcapsular areas the day after a single intravenous injection of 50 mg/kg of heparin.

Liver.—1 of 18 rats injected with 10 mg/kg of pentosan polysulfate sodium had a pale liver at 7 days following the last injection.

Lymph node.—Enlargement of the inguinal lymph node was observed in 2 of 18 rats 7 days after the last injection of 10 mg/kg of heparin.

Histopathology:

Kidney.—Histopathologic changes varied from an occasional atrophic tubule to many atrophic tubules associated with a moderate amount of chronic inflammatory response. The effect was seen only following subcutaneous injection of 10 mg/kg of either heparin or pento-

san polysulfate sodium with an approximate equal incidence after either compound. Even 1 of 12 subcutaneous saline control rats had many atrophic tubules associated with a moderate amount of chronic inflammatory response.

Skin.—Hemorrhagic cysts were present in the 10 mg/kg subcutaneous heparin group in 2 of 6 rats sacrificed at seven days following the last injection.

Histochemistry: Very little metachromatic staining occurred in the tissues studied in this investigation. The aldehyde fuchsin preparations were too weak to be evaluated with a microdensitometer.

Values are given for the determination of metachromatic substances using toluidine blue. The values are what this reviewer presumes to be low values and as such are subjected to much variation. For example, a range of 0.00 to 0.98 on a scaling index occurred for the spleens taken from a group of six rats examined 7 days after a single 50mg/kg dose of pentosan polysulfate sodium. Only 1 of 60 comparisons of the two drugs at different routes and sacrifice periods showed any significant statistical difference. Heparin on the first day following a single intravenous dose of 50 mg/kg caused a significant increase in metachromatic substance over a similar dose of pentosan polysulfate sodium at the same time period.

Conclusion: Neither heparin or pentosan polysulfate resulted in retention of any statistical significance in the tissues examined at the dosage and routes of administration employed in this study.

2. Pharmacokinetic studies with ³H-pentosan polysulfate in rabbits :

Study Number: 38

Test Material: Defined only as ³H-pentosan polysulfate with an average degree of sulfatation of 1.9 and a molecular mass of 4700 Daltons for the major fraction.

Procedure: Four rabbits (Group 1) received 5 mg/kg of the labeled compound as a single i.v. bolus in the marginal ear vein.

Four rabbits (Group 2) received the 5 mg/kg bolus as above but were then supplemented with a continuous

infusion of the labeled compound at 2.5 mg/kg/hr for 2 hours. Results: Following a single bolus (Group 1), the half-life for the α -phase was 20 minutes and for the β -phase 129 minutes. Following a single bolus plus continuous infusion for two hours (Group 2), a declining straight-line relationship occurred between blood plasma concentration and time over a 6-hour observation period giving a half-life (129 minutes) identical to the β -phase following a single bolus. Peak blood plasma concentration of pentosan polysulfate immediately after the bolus injection was 50.4 μ g/mL.

Within six hours, 31% of the administered dose was excreted in the urine.

Literature Reference: Richter M, Pharmazie 42: 699-670, 1987.

3. Absorption, distribution, and excretion of ^{35} S labeled SP-54 in the rat :

Reference Study Number: 43

Test Material: Labeled SP 54 was supplied by
It was prepared by
reacting pentosan with radioactive chlorosulfuric acid.
The test material contained up to 3% inorganic ^{35} S-sulfate.

Strain of Rats: Wistar

Number of Animals/Group: 2 or 3

Dosages: 0.05 to 100 mg/kg intravenously
0.05 to 80 mg/kg intramuscularly
10 and 100 mg/kg orally

Follow-up: 1 minute to 14 weeks

Plasma Levels Following 50 mg/kg Intravenously:

<u>Time</u>	<u>μg/g of Plasma</u>
1 min	
1 hr	
12 hr	
24 hr	
14 wk	

Results Following 50 mg/kg Intravenously: By 60 days post-

administration, 60% of the activity is excreted in the urine and 15% is excreted in the feces. Another 5% was found in the liver and kidneys, with the 10% in the rest of the body.

Whole Body Autoradiography After I.V. Administration of 100 Mg/Kg: One hour after injection the kidney showed exceptional activity and a high activity was present in the small intestine and proximal large intestine. After 12 hours, the kidney was still the organ with the highest activity, followed by the distal large intestine, liver, spleen, fascia, perichondrium, and bone marrow. After 24 hours, the adrenal cortex, liver, spleen, and distal end of the large intestine were still strongly active. The strongly blackened marrow of the vertebrae was strongly contrasted against the vertebrae and the intervertebral disc.

After one week, the kidney, liver, and spleen stood out clearly. Not the contents but the walls of the intestinal tract remained visible.

After four weeks, the kidney, liver, spleen, and intestinal wall as well as the fascia and bone marrow showed distinct black areas.

Microautoradiography of the Kidney: Twelve hours after the i.v. injection of 100 mg/kg of ³⁵S-SP 54 the reduction of activity in the kidney medulla, compared to the 1 hour value, was most noticeable. In contrast to the less active medulla, the blackening of the renal cortex after 12 hours was rather more intense. Virtually all the proximal convoluted tubules were affected by radioactivity: the terminal main pieces of the outer strip were light and became lighter, especially towards the medulla.

Four weeks after i.v. injection with the radiolabeled compound the activity in the region of the renal cortex was markedly reduced and the proximal convolutions did not stain as a whole anymore. Singular black figures were seen which corresponded to the collection tubules or thick parts of the Loop of Henle.

Microautoradiography of the Liver: An increased black staining over the hepatocytes occurred at 24 hours when compared with that which was present at 1 hour. The picture was dominated by numerous black areas distributed throughout all liver lobes and represented the von Kupffer cells.

After four weeks, the intensity of the radioactivity had gradually decreased over the von Kupffer cells and the hepatocytes showed virtually background activity.

Microautoradiography of the Spleen: The splenic capsule and trabeculae contained more radioactivity than the parenchyma one hour after i.v. injection of 100 mg/kg of the radiolabeled compound.

The activity decreased 12 hours after injection in the region of the lymph follicles, but it increased in the red pulp. A rim of blackened cells was present around the lymph follicles.

At one and four weeks, there is little change from 12 hours except for a general decrease in activity. At this time period the individual cells within the red pulp became visible and were probably reticulum cells.

Comparison of "Organic" and Inorganic Sulfate Activity:
Thirty minutes after an i.m. injection, 95% organic and 3-5% inorganic activity were found in the plasma. When 10 mg/kg and 1 mg/kg of the labeled compound were administered, the 12 hour values for organic activity were 63% and 39% respectively. The values for urine were not significantly different from those for plasma. After 30-48 hours, there was only 40% organic and 60% inorganic activity in the urine.

Oral Administration of ³⁵S-Pentosan Polysulfate Sodium:

Oral Dose (Mg/Kg)	Time	SP 54 Equivalents (µg/mL)	
		Plasma	Urine
10	30 Min		
	2 Hrs		
	4 Hrs		
	12 Hrs		
	0-4 Hrs		
	4-12 Hrs		
	30-48 Hrs		
100	30 Min		
	2 Hrs		
	12 Hrs		
	0-12 Hrs		
	30-48 Hrs		

4. Pharmacokinetics in rats after oral and parenteral administration

Study Number: 42

Test Material: ³H-Pentosan polysulfate sodium with a specific radioactivity of 736 μ Curie/g was supplied by

No. of Animals/Route: 3M & 3F

Dosage per Route: 25 mg/kg single dose.

Plasma Concentration of Non-volatile Radioactivity:

<u>Route</u>	<u>Time</u>	<u>Mean Peak Value</u> <u>μg Equiv./mL</u>
Intravenous	2 min.	198
Subcutaneous	15-30 min.	68.6
Intraperitoneal	1 hour	53.2
Oral	30 min.	0.24
Rectal	30 min.	1.71

Urinary excretion:

<u>Route</u>	<u>‡ Administered Dose</u> <u>at 72 Hours</u>
Intravenous	40
Subcutaneous	31
Intraperitoneal	19
Oral	0.6
Rectal	6.1

Three male rats in addition to the rats used in the plasma concentration studies were utilized in the urinary excretion study. When the total amount of radioactivity excreted into the urine following parenteral administration was considered, the major portion (66-93%) was excreted in the first 8 hours. The high values in the urinary excretion study following rectal administration were thought to be the result of contamination of urine samples with administered drug.

Pharmacokinetics: Apparent half-life of pentosan polysulfate sodium following intravenous administration was about 3 hours. Apparent terminal elimination half-lives after 24 hours were 14, 30, and 20 hours respectively for the intravenous, subcutaneous, and intraperitoneal routes. The total urinary clearance was, on average, less than the total plasma clearance and indicated elimination processes other than urinary

5. Oral administration of ³H-pentosan polysulfate sodium to the rat—single dose :

Study Number: 40

Test Material: ³H-pentosan polysulfate sodium was supplied by _____ and had a specific radioactivity of 18.7 μ Ci/mg. The non-radiolabeled product was SP 54. The radio-chemical purity of the labeled product was 96.8%.

Strain: Pigmented rats of the PVG strain

Number of Animals/Level:

Excretion study 3 M & 3 F
Distribution study 20 M & 20 F

Dosage Level (Mg/Kg): "Nominal" 10

Duration and Route: A single dose by oral gavage

Results of Excretion Study:

<u>Sample Type</u>	<u>Collection Time</u>	<u>Mean Percent of Radio-activity Dose Recovered</u>	
		M	F
Urine	168 Hrs	5.0	3.8
Feces	168 Hrs	89.6	88.5
Cage washings	168 Hrs	<0.1	<0.1
Carcass	168 Hrs	0.1	0.1
Total	168 Hrs	94.7	92.4

Oral absorption when calculated on the basis of urinary excretion, ranged from 3.6 to 5.0 %.

Results of Tissue Distribution Study:

<u>Tissue</u>	<u>Mean μg Equivalents/g Tissue</u>					
	<u>1.5 Hr</u>		<u>6 Hr</u>		<u>168 Hr</u>	
	M	F	M	F	M	F
Liver	0.61	0.60	0.88	0.52	0.13	0.22
Kidneys	1.87	1.06	2.29	1.14	0.32	0.50
Lungs	0.26	0.20	0.17	0.12	0.01	0.01
Spleen	0.27	0.39	0.27	0.23	0.06	0.10
Adrenals	0.35	0.31	0.14	0.08	N.D.	0.04
Thyroids	0.24	0.28	0.17	0.10	0.01	N.D.
Stomach	8.31	3.18	3.11	0.42	0.01	0.02
Ileum	15.0	5.95	1.49	0.37	0.05	0.05
Colon	14.8	22.8	16.4	11.9	0.07	0.10
*Plasma	0.20	0.19	0.22	0.23	0.05	0.06
**Plasma	0.09	0.06	0.05	0.04	0.01	N.D.
Bone	0.16	0.18	0.11	0.05	0.02	0.02

N.D. Not detected *Volatile plus non-volatile ³H
**Freeze-dried samples

Ninety minutes after dosing the highest mean concentra-

tions were found in the colon, ileum, stomach, kidneys, liver, and spleen.

After six hours, concentrations fell rapidly in all tissues except for liver, kidney, and spleen. After 168 hours, the liver was found to have the highest concentration (0.63% of the dose). Volatile radioactive measurements accounted for 0.59 to 0.69% of the dose, indicating that the tritium label was relatively non-labile.

Maximum plasma levels were reached 30 minutes post administration and the terminal elimination half-life of total radioactivity was 72 hour for males and 106 hours for females.

6. Elimination of ³H-pentosan polysulfate sodium after single and repeated oral administration to rats :

Study Number: 41

Test Material: ³H-pentosan polysulfate sodium was supplied by _____ and had a specific radioactivity of 18.7 μ Ci/mg. The non-radiolabeled product was SP 54. The test article was dissolved in distilled water to a concentration of 2 mg/mL. The radiochemical purity of the labeled compound was 95.7%.

Strain: Pigmented rats of the PVG strain

Number of Animals: Single dose 8 males
 Repeated dose 8 males

Dosage Level: 10 mg/kg for single and repeated dosages

Duration and Route: Animals received either a single dose or 14 consecutive daily doses of ³H-SP 54 by oral gavage.

Results:

Concentrations of Non-Volatile Radioactivity in Plasma at 3 Hr after a Single and 14 Daily Oral Doses of ³H-SP 54 (10 mg/kg to Male Rats)

<u>Sample Type</u>	<u>Mean μg Equivalent ³H-SP 54/mL</u>	
	<u>Single Dose</u>	<u>14 Doses</u>
Venous plasma	0.111	0.203

Arterial plasma 0.111 0.201

Concentrations of Non-Volatile Radioactivity in Tissue Endothelia at 3 Hr after a Single and 14 Daily Oral Doses of ³H-SP 54 (10 mg/kg) to Male Rats

<u>Sample Type</u>	<u>Mean µg Equivalents ³H-SP 54/cm² Tissue</u>	
	<u>Single Dose</u>	<u>14 Doses</u>
Vena cava	2.4	0.8
Aorta	0.6	0.5
Bladder	34.3	19.3

Concentrations of Non-Volatile Radioactivity in Tissues* at 3 Hr after a Single and 14 Daily Oral Doses of ³H-SP-54 (10 mg/kg) to Male Rats

<u>Sample Type</u>	<u>Mean µg Equivalents ³H-SP 54/ g tissue</u>	
	<u>Single Dose</u>	<u>14 Doses</u>
Vena cava	1.063	1.761
Aorta	0.143	0.511
Bladder	3.107	3.084

*Tissues analyzed for radioactivity following removal of Endothelia

Percent of Total Radioactivity Recovered in Urine Following 13 Oral Doses of ³H-SP 54 (10 mg/kg) to Male Rats

<u>Number of Doses</u>	<u>Mean % Radioactive Dose Recovered</u>
1	5.1
2	6.3
3	6.2
6	4.8
8	5.0
13	6.6

Up to 0.8% of the daily administered radioactivity present in the urine was volatile.

Radiolabeled Metabolites in Urine Following Repeated Daily Oral Administration of ³H-SP 54 (10 mg/kg)

<u>Number of Doses</u>	<u>*Mean % of Urinary Radioactivity</u>		
	<u>³H-SP 54</u>	<u>Fraction 1</u>	<u>Fraction 2</u>
1	5.4	89.3	5.4
3	18.2	71.2	10.8

7	17.9	70.1	12.1
13	13.4	59.6	27.0

*Expressed as a percent of urinary radioactivity recovered from each gel-filtration column. Results are the average of the means from two studies.

Elimination of unchanged ³H-pentosan polysulfate sodium in the urine reached a steady state by Day 3 of treatment. Most of the radioactivity was confined to two bands. Fraction 1 was a narrow band with a prominent peak whereas Fraction 2 was a wider band with a much lower peak. A reversal of radioactivity occurred with the amount in Fraction 1 declining and the amount in Fraction 2 increasing with progression of time.

7. Preferential localization of ³H-pentosan polysulfate sodium to urinary tract in rats :

Study Number: 44

Test Material: Unlabeled product was obtained from and tritiated by
Specific activity was 0.6 mCurie and the radiochemical purity was 98%.

Strain: Sprague-Dawley

Protocol:

<u>No. of Female Rats</u>	<u>Treatment</u>
2	Injected with 1 mCurie intravenously and sacrificed 1 hr later
2	Administration of 1 mCurie by oral gavage and sacrificed 4 hr later
2	Bladder of the anesthetized animal was washed with water, then 0.2 mCurie instilled into the bladder
2	Bladder of the anesthetized animal was washed with 0.5 mL of 0.4 N HCl, then 0.2 mCurie instilled into the bladder

Results:

a. Whole-body autoradiography.—One hour after intravenous injection of ³H-pentosan polysulfate sodium, the

radioactivity was distributed extensively in the whole animal with a notable labeling of connective tissues. The liver had a higher concentration than the blood and there was upper intestine activity, suggesting some hepatic excretion. A remarkably high activity was observed also in lymph nodes, especially in their periperal zone.

The highest activity (according to the investigators) in the body was found in the urinary tract, in the urine as well as the linings (probably in the epithelium) of the renal pelvis, ureter, and bladder.

Four hours after oral administration of the labeled compound, most of the activity appeared to be confined to the large intestine. Some activity was seen in liver and kidney, and especially in the lining of the ureter and in the contents and lining of the bladder.

- b. Intravesicular instillation into the bladder.—In control animals, not pretreated with HCl, deposition of the labeled compound for one minute resulted in the retention of radioactivity one hour later in a thick zone covering the bladder epithelium, and with a strong uptake in the epithelial lining. Pretreatment with 0.4 N HCl, in what is believed to be a correct interpretation of the results by this reviewer, resulted in a lowered uptake in the lining but higher uptake of radioactivity in the epithelium than in the water controls.
- c. Rinsing the bladder with sodium chloride.—After vigorous rinsing with saline, the radioactivity was still retained in the bladder wall. In other intravenous experiments, the bladder was exteriorized, everted, and rinsed in saline or urea of increasing osmolarity. High amounts of radioactivity (roughly 70%) could be washed off with 0.5 M saline. Rinsing the bladder wall with a 1 to 6% urea solution gave a 50% recovery of radioactivity compared with the saline extraction. Unchanged pentosan polysulfate sodium thus seems to be bound ionically with moderate strength.

REPRODUCTION STUDIES:

MOUSE:

Study Number: 33

Test Material: SP 54 (pentosan polysulfate sodium)

Dosage: Test material was administered daily as a subcutaneous dose of either 5 or 15 mg/kg from day 6 through day 15 of pregnancy.

Procedure: Segment II portion of the FDA guidelines of January 1966. 26-27 females were used per group.

Body Weight of Dams: Treated groups paralleled controls.

Results:

	Dose (Mg/Kg)		
	0	5	15
No. of Pregnant Females	23	22	23
No. of Implantations & Resorptions	262	263	273
No. of Viable Young	6.1	9.5	6.6
Mean Litter Size	245	238	255
Mean Pup Weight (g)	10.7	10.8	11.1
No. of Abnormal Fetuses	1.04	0.99	1.09
	1 ^a	0	3 ^b

^aCleft palate

^bOne fetus with fusion of 6th and 7th ribs, one fetus with exencephaly, and one fetus hernia of left lateral abdominal wall.

RAT:

Study Number: 31

Test Material: SP 54 (pentosan polysulfate sodium)

Procedure: Study was performed in 1963 prior to FDA's guideline. Twenty male and 20 female Wistar rats received intraperitoneal injections of 20 mg/kg SP 54 initially for three weeks (except Sundays) with a reduction to 10 mg/kg for another week (except Sunday). At the end of the treatment period, males were placed with the females for 14 days before separation of the sexes. Twenty male and 20 female rats received control intraperitoneal injections of saline. Number

of females in the treated and control groups reduced to 14 animals each at the conclusion of the mating period.

Growth: Treated group paralleled control group.

Mortality: 1 of 14 in each of the treated and control groups of female rats.

Clinical Observations: During the pretreatment period with a dosage of 20 mg/kg many male animals showed a dark blue discoloration of the skin of the scrotum, which gave rise to the conclusion that hemorrhages into the peritoneal cavity had occurred.

Reproduction Performance:

	Mg/Kg SP 54	
	Q	<u>20-10</u>
No. of Pregnancies	14	14
No. of Young/Litter	8.36	8.86
% Alive First Few Hours*	93	81
No. Days Between Mating and Birth	24.93	24.29

*One pup cannibalized in control group and six in treated group.

RAT:

Study Number: 32

Test Material: SP 54 (pentosan polysulfate sodium)

Procedure: Study was performed in 1963 prior to FDA's guideline. Six times a week 10 mg/kg SP 54 was injected into the musculature of the upper thigh of 24 male rats and 24 female Wistar rats. The shots were given alternately into the right and the left thigh. Treatment was conducted for 85 days followed by an observation period for an overall total of 116 days. Four weeks after the beginning of treatment, males were caged with females and treatment was continued for 14 more days. At this time males were separated from the females. A control group consisted of 24 males and 24 females that received an equal volume of physiological saline as the treated group.

Growth: Treated males lagged 8% in weight gain behind their

control counterparts.

Mortality: One female each in the control and test groups.

Reproduction Performance:

	Mg/Kg SP 54	
	<u>0</u>	<u>10</u>
No. of Females	23	23
No. of Pregnancies	20	20
No. of Offspring	205	225
No. of Stillbirths	6	21
‡ Stillbirths	2.9	9.3
No. Pups/Litter	10.25	11.25
No. Deaths between Birth and 30 Days	17	40
Mean Wt. Pups at 5 Days(g)	11.5	8.5

RAT:

Study Number: 35

Test Material: SP 54 (pentosan polysulfate sodium)

Strain: Charles River CD

Dosage: Pentosan polysulfate sodium was administered daily as a subcutaneous dose of either 5 or 15 mg/kg. Dosing commenced on day 15 of pregnancy and continued daily until day 21 post partum.

Volume of Injecion: 1 mL/kg

Procedure: Segment III portion of the FDA Guidelines of January 1966. 22 pregnant females were used per group.

Body Weight of Dams: Treated groups paralleled controls.

Results:

	Dose (Mg/Kg)		
	<u>0</u>	<u>5</u>	<u>15</u>
No. of Pregnant Females	22	22	20
Medium Gestation Duration (days)	22	22	22
No. of Viable Young at Birth	189	203	183
‡ Stillborn	2.1	1.0	2.1
Mean Viable Litter Size	8.6	9.2	9.2
Mean Pup Weight at Birth (g)	7.0	6.7	6.6
‡ Survival at 21 days	98	93	90
Mean Pup Weight at 21 days (g)	58.4	51.4	55.8

No abnormal pups were observed, and no unusual behavior was noted.

RABBIT (New Zealand White):

Study Number: 34

Test Material: SP 54 (pentosan polysulfate sodium)

Dosage: Pentosan polysulfate sodium was administered subcutaneously commencing on day 6 of pregnancy and continued daily up to and including day 18 of pregnancy.

Procedure: Segment II portion of the FDA Guidelines of January 1966. 12 pregnant females were used for group. Each rabbit was injected intravenously with 10 i.u. of luteinizing hormone to ensure that ovulation took place. On day 29 of pregnancy the animals were sacrificed.

Volume of Injection: 0.25 mL/kg

Body Weight of Dams: Treated dams showed marginal but persistent retardation of bodyweight gain. The response was more noticeable at 7.5 mg/kg.

Results :

	Dose (Mg/Kg)		
	0 ^a	2.0	7.5
No. of Pregnant Females	11	12	12
No. of Corpora Lutea	112	123	112
No. of Implantations	98	114	98
‡ Ova Implanted	88	93	88
‡ Resorptions	7.1	11	31
No. of Viable Young	91	102	68
Mean Viable Litter Size	8.3	8.5	5.7
Mean Fetal Weight (g)	40	39	34
Major Abnormalities	0	1 ^b	0
Minor Abnormalities	2 ^c	0	10 ^d

^aOne dam excluded, agenesis of right uterine horn

^bMultiple skeletal abnormalities

^cOne agenesis of the gall bladder, one agenesis of intermediate lung lobe.

^dOne agenesis of the gall bladder, eight with bilateral ocular opacity, one with bilateral ocular opacity and also asymmetrical and fused third, fourth, and fifth sternbrae, one agenesis of gall bladder plus fusion of sternbrae one to five and sutural bone.

Clinical Signs: There were no obvious signs of systemic or local reaction around injection sites among animals receiving 2 mg/kg. Several animals dosed with 7.5 mg/kg exhibited anorexia towards the end of, and subsequent to, the dosing period.

TRANSPLACENTAL TRANSFER OF RADIOACTIVE DRUG

Tritiated sodium pentosanpolysulfate was administered as a single intramuscular dose to 20-day old pregnant rats at a level of 25 mg/kg. Two animals were sacrificed at 2 hours and another two rats at 6 hours after drug administration.

Rat No.	No. of Fetuses	Time (Hours)	Mean Mcgm Drug per g Fetus	Mean Mcgm Equiv. of Drug per g Placenta
	16	2	0.204	20.7
	14	2	0.235	25.2
	16	6	0.144	20.4
	16	6	0.109	19.5

Distribution of radioactivity in the dam following a single intramuscular injection of labeled pentosanpolysulfate was as follows:

Rat No.	Time (Hours)	Liver	Kidney	Blood	Plasma
	2	50300	251000	48000	56020
	2	52800	271000	53400	59400
	6	115000	485000	8080	9370
	6	91500	387600	5990	6290

MUTAGENIC STUDIES (Ref. Firm 1):

1. Micronucleus test—NMRI mice were randomized into five groups of ten animals each (five males and five females) and treated as follows:

Group	Substance	Dose (Mg/Kg)*
1	Sodium Chloride Injection	Control
2**	Cyclophosphamide	100
3	Pentosanpolysulfate	9
4	Pentosanpolysulfate	90
5	Pentosanpolysulfate	900

*Two doses as designated spaced 24 hours apart.

****Positive control.**

Two intraperitoneal injections were made in volumes of 10 mL/kg at an interval of 24 hours. Six hours after the second injection, the animals were sacrificed and the femoral bone exposed.

Bone marrow smears were made and the number of micronucleus-containing polychromatic erythrocytes were counted. Results were as follows:

Dose* (Mg/Kg)	Number of Micronucleus-containing Polychromatic Erythrocytes					
	Total		Mean		Median	
	(M)	(F)	(M)	(F)	(M)	(F)
Neg. Control	11	13	2.2	2.6	2	3
Pos. Control	120	118	24.0	23.6	24	24
9	11	11	2.2	2.2	2	2
90	13	14	2.6	2.8	3	3
900	14	14	2.8	2.8	3	2

*Two doses as designated spaced 24 hours apart

2. Ames assay.—The Salmonella typhimurium histidine reversion system is a microbial assay which measures his-/his+ reversion by chemicals which cause base changes or frame shift mutations in the genome of this organism. Results of the assay with and without S9-fraction from rat liver are as shown in the following tables. Positive controls were included to verify the authenticity and sensitivity of the assay.

Results without S9-mix:

Test Substance Concentration/ Plate	Mean Number of His+ Revertant Colonies				
	TA 1535	TA 1537	TA 1538	TA 98	TA 100
Mg					
10	19	91	13	12	144
2	16	125	24	5	854
0.5	27	161	19	18	148
0.1	18	96	16	12	157
0.01	20	68	13	9	156
Control	21	105	15	17	138

Results with S9-mix:

Test Substance Concentration/ Plate	Mean Number of His+ Revertant Colonies				
	TA 1535	TA 1537	TA 1538	TA 98	TA 100
10	14	24	27	33	127
2	16	21	29	37	151
0.5	19	25	28	41	139
0.1	16	31	25	40	147
0.01	19	32	30	41	141
Control	18	30	34	47	174

LITERATURE STUDIES NOT CITED BY SPONSOR:

1. Effect of pentosanpolysulfate (SP 54) on fibrinolytic enzyme system:

Man.—Single doses of SP 54 (500 mg p.o. or 50 mg s.c.) significantly increased euglobulin lysis time activity in 6 healthy male subjects (mean age 22.1 yr, range 19-30). Treatment with multiple doses of p.o. SP 54 (500 mg/day for 5 days) elicited a significant increase in fibrinolytic activity over placebo.

Rats.—Single doses s.c or i.m. of SP 54 (6 mg/kg) prevented fibrinolytic shutdown following surgery. In rats with inferior vena cava induced by ligation, a single dose of 10 mg/kg SP 54 s.c. reduced clot weight from 2.92 to 1.13 mg after 4.5 hr (Marsh NA et al, Thromb Haemostasis 54: 833-37, 1985).

2. Pentosanpolysulfate (SP 54) induced thrombocytopenia:

A 52-yr-old woman was given SP 54 (21 mg i.m. x 2/day) following perineal surgery, as prophylaxis for deep vein thrombosis. On the 9th post-operative day, she developed a sudden occlusion of popliteal artery. Platelet count, which was normal on admission, was found to be decreased: 56,000 per microliter. SP 54 therapy was discontinued and heparin (400 units per-kg/day) was substituted. During the following days arterial ischemia persisted and platelet count dropped to 17,000 per microliter. On the 13th post-operative day, the diagnosis of SP 54 (and then heparin) induced thrombocytopenia was suspected, and heparin therapy was discontinued. After acenocoumarol and aspirin, clinical and

ultra-sound signs of arterial ischemia rapidly resolved, and platelet count increased to normal values by 48 hours. Both heparin and SP 54 were capable of inducing platelet aggregation in vitro experiments, whereas the saline control did not (Follea G et al, Thromb Haemostasis 34: 94, 1985).

3. Tolerance towards Pentosanpolysulfate (CB 8061) in human volunteers.—General tolerance in i.m. and s.c. CB 8061 (25, 50, 75, 100, and 150 mg by separate routes) was excellent in human volunteers, but mild pain occurred locally at the highest dosage. CB 8061 increased activated partial thromboplastin time, increased Quick's time, inhibited the activity of factor Xa and factor II and modified lipoprotein lipase activity. No fibrinolytic activity was observed although a mild proaggregant effect was seen (Thebault JJ et al, Thromb. Hemostasis 54:94, 1985).
4. Pentosanpolysulfate adjuvant treatment of transluminal angioplasty of the lower limb arteries.—Therapy consisted of 50 mg i.m. then at 50 mg i.m. for 3 days. Treatment with p.o. pentosanpolysulfate (300 mg/day) was continued for 12 months.

There were no immediate or late complications and no notable hematomas developed (Presse Med 15: 213,1986).

5. Treatment of interstitial cystitis with ELMIRON.—Eighty-seven patients with interstitial cystitis, for more than 2 years received ELMIRON at 200 mg b.i.d. p.o. for 6 months. Most patients responded favorably with reduction in pain and often within 4 weeks of treatment. There was a significant decrease in micturition frequency as well as an increase in mean voided volume in the group of patients without bladder ulcers while such changes could not be seen in patients with ulcers. At comparison patients with bladder ulcers had a smaller bladder capacity than those without. Patients with ulcers had a somewhat more intense pain before the treatment than those without, but both groups responded with relief of pain during treatment and pain reduction was stable at the 3 month follow up. At comparison of the cystoscopic findings before and after treatment there was a decrease in ulcer and petechial bleedings.

Fritjofsson A et al, Scand J Urol Nephrol 19 (Suppl 94): 50, 1985

6. Effect on hemostasis by a continuous 3-day infusion.—Ten cardiac patients received a continuous 3-day i.v. infusion of pentosanpolysulfate (4 mg/kg/day for 3 days) which did not modify bleeding time. Activated partial thromboplastin time, prothrombin time, and anti-Xa activity were most affected by the drug; factor V was decreased. There were no

adverse effects (deProst et al, Clin Pharmacol Ther 38: 171-75, 1985).

7. Inhibition of sodium urate crystal adherence to bladder surface by polysaccharide.—A study was conducted in rabbits anesthetized with rompum and ketamine to determine the effect of removal of bladder mucous with its contained glycosaminoglycan by means of HCl digestion and pretreatment with pentosan polysulfate sodium (PPS, Pharmacia) on adherence of radiolabeled urate crystals *in vivo*. There was a significant rise in crystal adherence in bladder stripped of mucous by instillation of HCl. This increase was counteracted by prior *in vivo* bladder instillation of PPS, or by previous *in vitro* incubation of the crystals with PPS.

Rabbits had their mucous digested with the instillation of 7 mL 0.6 N HCl for 1 min. This was followed by 15 mL of 20 mg/mL PPS instilled into the bladder for 30 min. All received 0.4 mL of labeled crystals with a fourth group receiving crystals pretreated with PPS which was retained in the bladder for 20 min. (Parsoins CL et al, J Urol 134: 514-16, 1985).

8. Pentosanpolysulfate on endothelial cell function.—This substance was tested for its effect on the growth of cultured bovine endothelial cells. At 10 mcg/mL it increased the growth rate without affecting incorporation of ³H-thymidine into DNA, while at 1 mg/mL pentosanpolysulfate inhibited growth. The material significantly increased plasminogen activator activity in the presence of serum factors, but did not stimulate the synthesis of prostaglandins (Delvos U, Klin Wochenschr 63 (Suppl 4): 17, 1985).

9. Role of pentosanpolysulfate (HEMOCLAR, CLIN-BYLA) in precipitating two thrombopenic incidents.—Twenty-one days after a 67-yr-old woman began treatment by injectable HEMOCLAR for a tibiotarsal sprain, superficial femoral thrombosis and thrombopenia (20,000/cu. mm) appeared. Thrombolysis was performed and followed by heparin therapy (30,000 IUK/24 hr), but recurrences necessitated surgical intervention twice and a further thrombolysis. The thrombopenia persisted until heparin was withdrawn.

"Following delivery a woman was treated for hemorrhoidal thrombosis by HEMOCLAR, given by injection for 5 days and lingually for 3 days. On the 8th day phlebitis appeared, necessitating heparin therapy. The platelet count, already declining, reached 65,000/cu.mm after 7 days on heparin, while the thrombosis spread. The thrombopenia returned to normal within 3 days of changing to antivitamin K treatment."

(Maiza D et al, Presse Md. 14:1289-90, 1985)

ADDITIONAL LITERATURE REFERENCES:

1. Rabbit model: Male rabbits were catheterized with a urinary catheter and the bladders prepared as follows: Group 1 (control) bladders were rinsed with three 15-ml aliquots of a phosphate buffered solution (pH 5.5). Group 2 (acid treated) bladders were rendered mucin deficient with 0.3 N HCl introduced via the catheter and left in the bladders for 1 minute. The acid was removed and the bladders rinsed with one 15-ml aliquots of phosphate buffer (pH 9.4) and then three 15-ml aliquots of pH 5.5 phosphate buffer. Group 3 (pentosan polysulfate sodium treated mucin deficient) bladders were rendered mucin deficient as described above. Then pentosan polysulfate sodium, 20 mg suspended in 1.0 ml of sterile distilled water, was placed into each bladder via the catheter, left for 30 minutes, and removed. After preparation as described above, each rabbit bladder received 1 mL of a bacterial suspension containing 10^5 colony forming units of E. coli via the catheter. Urine samples were obtained for bacterial counts at 48 hours post introduction.

Group	Urine from Bladders Showing	
	No Growth (%)	Bacterial Growth (%)*
(1) Control	28(78)	8(22)
(2) Acid-treated	18(53)	16(47)**
(3) Acid-treated plus ELMIRON	23(66)	12(34)

*Urine samples with greater than 10^4 bacteria per ml. ** $p < 0.02$. Numbers in parenthesis are percentage.

Parsons CL, J Urol 127: 167-9, 1982

2. Cell culture techniques in prenatal toxicity:

The technique used here was that of organ culturing. The term organ culture is used when a whole-organ anlage, or a representative part of it (e.g. a lobe of a lung or liver) is kept in culture, and growth—especially organ-specific differentiation—can be observed.

A culture technique suggested by Trowell was used in which limb buds from mouse embryos are kept on a filter or other support and the buds differentiate at the interface of the culture medium and the gas phase.

An abnormal development of limb buds was observed after the addition of pentosanpolysulfate to the culture medium (Neubert D, Pharmacol Ther 18: 397-434, 1982).

3. Treatment of human interstitial cystitis:

Pentosan polysulfate sodium was used in 3 female patients aged 29, 37, and 39 years, respectively. They complained of

a marked increase in frequency of micturition as well as pain in the bladder. At cystoscopy bleeding cracks in the mucosa were seen after normal fluid distension. Within 2 weeks of the start of treatment with pentosan polysulfate sodium 1 to 2 tablets 3 times daily, all patients reported improvement. The patient with the most severe symptoms responded best.

The investigator states that the drug has little or no anticoagulant effect, but that it does have anti-edema and anti-inflammatory action (Pollen JJ, S Afr Med J 50: 159, 1976).

EVALUATION:

Pentosan polysulfate has orphan drug status.

The urinary bladder secretes and binds to its surface a mucin layer composed in part by glycosaminoglycans (GAGs). These compounds, commonly known as mucopolysaccharides, are named from a coined word from glycosamine (amino sugar) and glycans (polysaccharides). Glycosaminoglycans, except hyaluronic acid, contain sulfate groups, that are linked by an ester bond to hydroxyl groups. Because of their carboxyl and sulfate groups, these biopolymers are highly negatively charged at physiological conditions. This makes the sulfonated GAGs extremely hydrophilic compounds that bind water molecules tightly to their sulfonated moieties. What develops, in essence, is a molecular layer of water between the transitional cell and its environment. When this compound is present on the mucosa, bacterial adherence to the cells and infection are reduced significantly.

The U.S. Adopted Name for this drug is pentosan polysulfate sodium. A more definitive name is sodium xylanpolysulfate, denoting the presence of xylose. Since glycosaminoglycans always contain a hexosamine, either D-glucosamine or D-galactosamine, the drug under consideration is not strictly a glycosaminoglycan.

Pentosan polysulfate sodium has had extensive marketing experience in Europe and Africa (13 countries), not especially for the indication proposed in the present NDA, but for the treatment and prophylaxis of thrombosis and hyperlipidemia. Two of the countries in which it is available are France and Germany. It has not been approved in the United Kingdom.

The applicant has designated those nonclinical animal studies which the firm considers as pivotal (Figure 1) and those which are considered only as supportive (Figure 2). The first study (Number 18) on the pivotal list is a 6-month's chronic toxicity study with pentosan polysulfate sodium in the diet of rats. The study contained 15 males and 15 females for each dosage group. The number of animals sacri-

Figure 1: Pivotal Multidose Studies

Species	Route	Duration	Title	Reference Study Number	Date	Conforms to GLP No
Rat	Oral Diet	6 Months plus recovery	Chronic Toxicity (6 Months) in Rats after Oral Uptake with Pentosan polysulfate sodium	18	1987	
Rat	S.C.	4 Weeks plus recovery	PZ 68 B: Toxicity in Subcutaneous Administration to Rats for Four Weeks with a Nine-Week Recovery Period	22	1979	✓
Rat	S.C.	26 Weeks plus recovery	Effects of SP 54 in Repeated Subcutaneous Administration to Rats for 26 Weeks	23	1969	•
Monkey	Oral (Gavage)	6 Months	Six Month Oral Toxicity Study in Rhesus Monkeys	25	1972	•
Monkey	S.C.	4 Weeks plus recovery	PZ 68 B: Four-Week Subcutaneous Toxicity in Baboons With a Five-Week Period of Recovery	27	1980	✓

*Predates GLP Regulations

Figure 2: Supporting Multidose Studies

Species	Route	Duration	Title	Reference Study Number	Date	Conforms to GLP No
Rat	Oral (Dietary)	1 Year	Chronic Toxicity of Sodium Pentosanpolysulfate (Dietary Administration for One Year)	19		
Rat	I.P.	3 Weeks plus recovery	Toxicological Investigation with the Compound SP 54 Subacute (21 Day) Study in Rats	20	1967	•
Rat	S.C.	14 Weeks plus recovery	Investigation of the Chronic Toxicity of Compound SP 54 in Rats	21	1968	•
Rabbit	S.C.	5 Weeks plus recovery	The Effects of SP 54 in Repeated Administration to Rabbits over Five Weeks	24	1969	•
Monkey	I.M.	21 Days	Investigation of the Subacute Toxicity of Compound SP 54 in Rhesus Monkeys	26	1968	•
Monkey	S.C.	13 Weeks plus recovery	SP 54 Parenteral Toxicity in Primates (Baboons) Repeated Injections for Three Months	28	1968	

*Predates GLP Regulations. **Report is not dated.

ficed at the end of the treatment period was 10 males and 10 females with the remainder allowed to recovery over a 3-month's period. Although the study was performed in 1987, it was done in East Germany and does not conform to GLP. A reversible leukopenia was observed in males at 4 and 17 times the clinical dose.

The most important study (Number 25) on the pivotal list in the reviewer's opinion is a 6-month's oral gavage study in rhesus monkeys by The study was done in 1972 and predates GLP regulations. Nevertheless, the study appears to be of good quality. Occult blood was regularly present in monkeys in the 200 mg/kg dosage group (approximately 33 times the clinical dose) and was roughly proportional to the degree of diarrhea. A trace amount of blood was present in 1 of 2 males at four months and 1 of 2 females after six months at 50 mg/kg (approximately 8 times the clinical dose). No grossly hemorrhagic foci could be visualized on careful examination of the entire gastrointestinal tract of any of the treated animals. Histopathologically, even the females in the low dosage group (2 mg/kg or 1/3 the clinical dose) had a possible increase in mucosal capillaries or inflammation and edema of the villous structure of the ileum. The colons of these same females had mucosal capillaries that were prominent and congested in the sub-mucosa. At the mid-dosage level (50 mg/kg), all four animals in the group had signs of mild or moderate congestion of capillaries in the gastrointestinal tract without evidence of hemorrhage. Dosing at 200 mg/kg resulted in sluggishness and weakness, accompanied by anemia and gastrointestinal bleeding and hematuria preceding death.

Another one-year dietary study (Number 19) in rats with pentosan polysulfate was listed as supportive information by the applicant. The study is undated, performed by the and does not conform to GLP. The French investigators did report that almost all animals that received 15 and 30 mg/kg had significant lesions in the intestinal mucosa. This involved extended areas of mucosal necrosis with ulcerations. The intestinal phenomenon was attributed to parasitic origin and enterobacteria. A similar "cage sickness" has been seen in both the investigator's colony and that of the supplier. If this last explanation is true, then it would seem that the lesions would also have been present in the high dosage (60 mg/kg) and control groups.

In one subcutaneous study (Study Number 21) lasting 14 weeks in rats, the most prominent feature was hepatic swelling at 5, 10, and 20 mg/kg. Only hepatic swelling and isolated vacuoles were seen at the lower dose. At both the 10 and 20 mg/kg doses, individual liver cells were involved again with vacuoles and hepatic swelling. Signs of regeneration were more prevalent at 10 mg/kg and rarely seen at 20 mg/kg. It

was noted in the study by (Study Number 23) that a few enlarged hepatocytes with marked cytoplasmic vacuolation still persisted when rats were injected subcutaneously for 26 weeks at 10 mg/kg and then allowed to recover in a 13-week withdrawal period. The amount of vacuolization and swelling was markedly less at the conclusion of the treatment period. Although the liver vacuoles had a close resemblance to fatty vacuoles, the histochemical preparation was shown to be almost fat free. When the liver was stained with toluidine blue, on the other hand, the pentosan polysulfuric acid ester of the dye could be demonstrated to be present metachromatically.

A toluidine blue positive material (Study Number 28) was deposited in the livers of baboons following the subcutaneous injection of pentosan polysulfate sodium in the 5 and 10 mg/kg groups. The amount of positive material was greater than in the 2 mg/kg and control groups. This same material was in the reticulo-endothelial cells after 13 weeks of dosing and still persisted in these cells for another 8 weeks following cessation of medication. These same baboons had 11 of 16 animals receiving subcutaneous injections of pentosan polysulfate sodium ranging from 2 to 10 mg/kg with variable degrees of atrophy of the cervical and/or mesenteric lymph nodes. None of the control animals were afflicted in this manner.

Another indication of the deposition of sodium pentosan polysulfate or a metabolic product in the liver was the increased mean relative weight of this organ when 10 mg/kg increased to 50 mg/kg was injected subcutaneously into baboons in the previously mentioned study over a 13-week period. Increases in the mean relative liver weight were seen at 2 and 5 mg/kg, but without statistical significance.

in a pharmacokinetic study (Number 42) predating GLP regulations observed the following results using radiolabeled ³H-pentosan polysulfate sodium:

Plasma Concentration of Non-volatile Radioactivity:

<u>Route</u>	<u>Time</u>	<u>Mean Peak Value</u> <u>µg Equiv./mL</u>
Intravenous	2 min.	198
Subcutaneous	15-30 min.	68.6
Intraperitoneal	1 hour	53.2
Oral	30 min.	0.24
Rectal	30 min.	1.71

Urinary excretion:

<u>Route</u>	<u>% Administered Dose at 72 Hours</u>
Intravenous	40
Subcutaneous	31
Intraperitoneal	19
Oral	0.6
Rectal	6.1

Apparent half-life of the radiolabeled compound following intravenous administration was about 3 hours in the first phase of elimination. In the second phase (after 24 hours), the half-lives were 14, 30, and 20 hours respectively for the intravenous, subcutaneous, and intraperitoneal routes. The investigators point out that the total urinary clearance was, on average, less than total plasma clearance and indicated elimination processes other than urinary excretion of unchanged drug.

A second excretion and tissue distribution study (Number 40) following a single 10 mg/kg oral dose of ³H-pentosan polysulfate sodium by gastric gavage to rats indicated that almost 90% of non-volatile radioactivity was recovered in the feces over a 168-hour period. Only 5% of the non-volatile radioactivity was recovered in the urine over this same time period.

The tissue distribution in this same study performed by , in 1983 following GLP regulations, revealed that 90 minutes following a single 10 mg/kg oral dose to rats, the highest concentrations of non-volatile radioactivity was in the colon, ileum, stomach, kidneys, liver, and spleen. After six hours, concentrations fell rapidly in all tissues except for liver, kidney, and spleen. After 7 days, the liver was found to have the highest concentration (0.63% of the dose).

An affinity for the urinary tract was seen in whole body autoradiography when rats were given an oral dose of radiolabeled pentosan polysulfate sodium (Odland B et al, Pharmacol & Tox 61: 162-166, 1987). While the distribution in urinary tissues was similar following either oral or intravenous administration of labeled compound, the amounts were greater following intravenous administration than that following oral administration.

Oral absorption of pentosan polysulfate sodium when based upon administration of the tritium labeled product to rats ranged from 3.6 to 5.0% when calculated on the basis of urinary excretion (Study Number 40).

The metabolism of pentosan polysulfate sodium in rats using the tritium labeled product has not been delineated. One group of investigators (Study Number 41) identified two

fractions in the urine besides unchanged pentosan polysulfate sodium when the tritium labeled product was given orally to rats. After a single 10 mg/kg dose the portion of the total radioactivity found in the urine as unchanged drug averaged about 5%. When the number of daily doses was increased to 13, the amount of unchanged drug increased to a mean of 13%. During this same interval, a reversal of radioactivity occurred with the amount in Fraction 1 declining and the amount in Fraction 2 increasing with the progression of time.

Solid pentosan polysulfate sodium when mixed with water and applied dermally as a paste at concentrations of 100 and 1000 mg/mL did not induce hypersensitivity in the guinea pig.

Study Number 33 contains a teratological (Segment II) study in mice by _____ that predates GLP regulations. No adverse effects were observed following the subcutaneous injection of pentosan polysulfate sodium at dosages as high as 15 mg/Kg. Likewise, a Segment III reproduction study in rats (Study Number 35) by the same investigators that again predates GLP regulations produced no adverse effects when the same route of administration and dosages were used. The most sensitive species was the rabbit by the same investigators (Study Number 34 that predates GLP). Increased resorptions and a smaller mean viable litter size were evident in a Segment II study at 7.5 mg/kg than that which was seen at 2.0 mg/kg or in the control animals. Two other studies (Numbers 32 and 32) are presented and both predate FDA reproduction guidelines of January 1966. The studies resemble more closely those of Segment I of the guidelines, but lack the quality possessed later by the Huntingdon studies. Comparison of the dosages in the animal reproduction studies with the recommended 200 mg per day or 6 mg/kg in a 50-kg individual is made difficult by the difference in the routes of administration. But based upon the theory that a greater bioavailability of pentosan polysulfate sodium occurs after parenteral exposure than that which occurs after oral exposure, no adverse effects to the human fetus are expected. Further, studies in the pregnant rat with radiolabeled pentosan polysulfate sodium would indicate that effective passage of the drug is blocked across the placental barrier.

On July 2, 1986, a letter was addressed to the sponsor of related IND _____ with the following comment concerning pentosan polysulfate sodium:

"A waiver of long term animal carcinogenic studies as a requirement for marketing under the orphan drug exclusivity of section 526 of the Federal Food, Drug, and Cosmetic Act is recommended by the division (HFD-160). In arriving at this decision, the close relationship of the active ingredient,

sodium pentosanpolysulfate to glycosaminoglycans occurring in many vertebrate connective tissues and fluids, such as skin, bone, cartilage, arterial walls, umbilical cord, vitreous humor, cornea, and synovial fluid was considered. Another factor is its lack of mutagenicity in the two studies by Battelle-Institut. Heparin, another glycosaminoglycan, has actually resulted in regression of Lewis lung tumor cells in mice (Folkman J, Pediatrics 84: 850-6, 1984)."

The common monosaccharide units of glycosaminoglycans found in nature are D-glucuronic acid, D-glucosamine, L-iduronic acid and D-galactosamine. Hyaluronic acid isolated from the vitreous humor of cattle eyes contains both N-acetyl-D-glucosamine and D-glucuronic acid in the glycosaminoglycan polymer. Heparin has glucosamine, L-iduronic acid, and D-glucuronic acid. Again pentosan polysulfate sodium resembles the glycosaminoglycans but has a 5-carbon monosaccharide instead of a 6-carbon monosaccharide and there is no amino or acetyl group in the molecule.

has conducted two mutagenic studies using pentosan polysulfate sodium (SP 54). Study Number 36 conducted in 1982 used Salmonella typhimurium in a reverse mutation assay according to Ames with and without the S9-fraction from rat liver. Study Number 37 conducted in the same year utilized the mouse micronucleus assay capable of detecting chromosome breaks. These two tests showed that pentosan polysulfate sodium had no potential for mutagenicity under the conditions of the tests.

In 1987, this Division made a request to the National Toxicology Program that pentosan polysulfate sodium be included among those chemicals scheduled for long term chronic toxicity/carcinogenic study. This reviewer has not seen any official notification but his understanding is that testing of the compound has been approved.

The reviewing chemist has requested a safety consideration of the fiber used for stuffing capsule bottles. The supplier,

states that purified rayon is used and that it conforms to the food additive regulations. Rayon is permitted under 21 CFR 177.2800 for use as articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food. Textiles and textile fibers used under this regulation are permitted for dry food only. Primary dermal irritation and subacute dermal sensitization information along with possible human safety data are contained in a Food Additive Petition (FAP 389). Merck Index defines rayon as regenerated cellulose that is produced almost exclusively by the viscose process. One of its uses is a surgical aid. Chemical Abstracts catalogs rayon under

6-20-87

acetate fibers. No adverse effects are expected when purified rayon is used as a stuffing material in capsule bottles.

The Precautions section of the package insert has no section on "Carcinogenesis, mutagenesis, impairment of fertility" as defined in 21 CFR 201.57. A recommended text for correcting the labeling is included under PHARMACOLOGY COMMENTS TO THE APPLICANT.

CONCLUSION:

Application is approvable from the standpoint of pharmacology with changes in the labeling.

The Precautions section of the package insert is missing a statement on "Carcinogenesis, mutagenesis, impairment of fertility" and the Pregnancy Category B section needs revision.

J. E. Wilson 12/20/91
James E. Wilson, Ph.D.

Linda M. DeWitt 12/20/91
P. B. Walter 12/22/91

C.C.
Orig. NDA 20-193
HFD-160/Document File
HFD-160/JEWilson
HFD-502/JWcissinger
HFD-160/MO/CRodriguez
HFD-160/Chem/PStewart
HFD-160/CSO/JRhee
HFD-345
R/D Init. by LMDewitt 12/19/91
F/T typed by JEWilson 12/20/91
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PHARMACOLOGY COMMENTS TO APPLICANT:

- 1. The following needs to be added to the Precautions section of the package insert in accordance with 21 CFR 201.57:**

- 2. The Pregnancy Category B section should be revised as follows:**

- 3. Please change the eighth word in the sentence under Nursing Mothers from**

N/A

Stat

JUL 16 1996

STATISTICAL REVIEW AND EVALUATION

NDA#: 20,193

SPONSOR: Baker Norton Pharmaceuticals, Inc.

DRUG: Elmiron® (Pentosan Polysulfate)

INDICATION: Treatment of Interstitial Cystitis

DOCUMENTS REVIEWED: Submission dated April 10, 1996

DATE: Date received by Medical Division (Stamp Date): 4/11/96
Date received by Division of Biometrics: 5/2/96

MEDICAL REVIEWER: L. Paserchia, M.D.

STATISTICAL REVIEWER: R. Davi, M.S.

MAJOR REVIEW ISSUE:

- This statistical review concentrates on the relationship between the occurrence of adverse events and the patients' age, gender, and race.

The sponsor has responded to this product's FDA approvable letter dated March 1, 1996. Of the requests made by FDA in the approvable letter, the request for a demographic subset analysis for safety (age, race, and gender) is the only request which is statistical in nature. Therefore, this review will concentrate specifically on the sponsor's response to this request.

The sponsor submitted tables containing the frequency with which different types of adverse events occurred in each demographic subgroup. The events were grouped by 12 major body systems including the following: body as a whole, cardiovascular system, digestive system, endocrine system, hemic/lymphatic system, metabolic/nutritional system, musculoskeletal system, nervous system, respiratory system, skin and appendages, special senses, and urogenital system. Three such tables, one for each of E001, E002, and the Open-labeled Physician Usage Study were submitted. However, since the sample sizes in Studies E001 and E002 are fairly small (in comparison to the open-labeled physician usage study) and adverse events occur fairly infrequently, finding statistically significant results concerning safety for these studies is not possible. Therefore the interpretation of the adverse events tables corresponding to Studies E001 and E002 is left to clinical judgement. Because of the large sample size involved in the open-labeled

physicians usage study, formal statistical hypothesis testing is possible to assess the relationship between the occurrence of an adverse event and the demographic subgroups. The sponsor's listing of which adverse events occurred in each demographic subgroup for the open-labeled physicians usage study is contained in Appendix A for the reader's reference. Table 1 below contains the frequency and proportion of adverse events which occurred by body system and demographic subgroup.

Table 1: Frequency and Proportion of Adverse Events by Body System and Demographic Subgroup*

Body System	Age		Gender		Race	
	17-60 yrs N = 2155	61-88 yrs N = 651	male N = 287	female N = 2523	white N = 2643	nonwhite N = 70
Body as a Whole	231, 10.72%	49, 7.53%	14, 4.88%	266, 10.54%	272, 10.29%	4, 5.71%
Cardiovascular System	37, 1.72%	17, 2.61%	13, 4.53%	41, 1.63%	51, 1.93%	3, 4.29%
Digestive System	279, 12.95%	75, 11.52%	27, 9.41%	327, 12.96%	336, 12.71%	9, 12.86%
Endocrine System	6, 0.28%	0, 0.00%	0, 0.00%	6, 0.24%	5, 0.19%	0, 0.00%
Hemic/Lymphatic System	45, 2.09%	17, 2.61%	6, 2.09%	56, 2.22%	59, 2.23%	1, 1.43%
Metabolic/Nutritional	55, 2.55%	13, 2.00%	8, 2.79%	60, 2.38%	63, 2.38%	2, 2.86%
Musculoskeletal System	25, 1.16%	7, 1.08%	2, 0.70%	30, 1.19%	31, 1.17%	0, 0.00%
Nervous System	79, 3.67%	20, 3.07%	9, 3.14%	90, 3.57%	94, 3.56%	5, 7.14%
Respiratory System	37, 1.72%	9, 1.38%	3, 1.05%	43, 1.70%	44, 1.66%	1, 1.43%
Skin and Appendages	171, 7.94%	50, 7.68%	7, 2.44%	211, 8.48%	206, 7.79%	10, 14.29%
Special Senses	28, 1.30%	12, 1.84%	5, 1.74%	35, 1.39%	38, 1.44%	1, 1.43%
Urogenital System	88, 4.08%	16, 2.46%	8, 2.79%	96, 3.80%	101, 3.82%	2, 2.86%

* This table of adverse events by body system was summarized using the sponsor's more detailed adverse event table included in Appendix A for reference.

For each body system, a Chi-square test was used by this reviewer to determine if a statistically significant relationship between an adverse event occurring and being in a certain demographic subgroup existed. The four pairs of boxes which are shaded in Table 1 are the comparisons which were found to be statistically significantly different. The four statistically significant relationships and their p-values are discussed further below. It should be noted that when 36 statistical hypothesis tests (multiple comparisons) are conducted (as was in this analysis), finding four statistically significant comparisons is not unreasonable even when

there is no true difference present.

Relationship Between an Adverse Event Occurring in the Body as a Whole and Age:

When the proportion of patients who experienced an adverse event in the body as a whole was compared for the subjects who were ages 17 to 60 years of age and to the same such subjects who were ages 61 to 88 years of age, a statistically significant relationship was found. In this study, the chances of incurring an adverse event in the body as a whole is statistically significantly higher in the 17 to 60 year old age bracket than in the 61 to 88 year old age bracket (10.72% in the 17-60 year olds, 5.73% in the 61-88 year olds, p -value=0.017). Further examination of the specific adverse events listed as events in the body as a whole revealed that this relationship was being driven by the fact that a statistically significant higher proportion of 17-60 year olds than 61-88 year olds reported experiencing headaches (3.62% in the 17-60 year olds, 0.61% in the 61-88 year olds, p -value<0.001). It should be noted that when examining specific adverse events which occurred very infrequently, determining whether there was a statistically meaningful difference in the demographic groups was not possible.

Relationship Between an Adverse Event Occurring in the Body as a Whole and Gender:

When the proportions of males and females who experienced an adverse event in the body as a whole were compared, a statistically significant relationship was found. In this study, the chances of incurring an adverse event in the body as a whole is statistically significantly higher for females than for males (10.54% for females, 4.88% for males, p -value = 0.002). Further examination of the specific adverse events listed as events in the body as a whole revealed that this relationship was being driven by the fact that a statistically significant higher proportion of females than males reported experiencing headaches (3.21% for females, 0.35% for males, p -value = 0.006).

Relationship Between an Adverse Event Occurring in the Cardiovascular System and Gender:

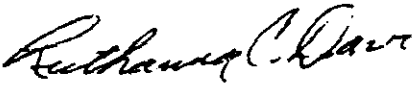
When the proportions of males and females who experienced an adverse event in the cardiovascular system were compared, a statistically significant relationship was found. In this study, the chances of incurring an adverse event in the cardiovascular system is statistically significantly higher for males than for females (1.63% for females, 4.53% for males, p -value = 0.001). Due to the low incidence of each specific adverse event in this body system, a "key event" responsible for driving this relationship could not be identified.

Relationship Between an Adverse Event Occurring in the Skin and Appendages Category and Gender:

When the proportions of males and females who experienced an adverse event in

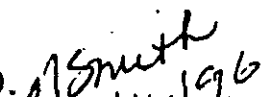
the skin and appendages category were compared, a statistically significant relationship was found. In this study, the chances of incurring an adverse event in the skin and appendages category is statistically significantly higher for females than for males (8.48% for females, 2.44% for males, p-value = 0.000). Further examination of the specific adverse events listed as events in the skin and appendages category revealed that this relationship was being driven by the fact that a statistically significant higher proportion of females than males reported experiencing alopecia (4.28% for females, 0.70% for males, p-value = 0.003).

The reader should note that although the four relationships mentioned above were statistically significant correlations, this analysis does not indicate that Elmiron was *causing* any of these relationships. For example, the relationship between a cardiovascular event and being male most likely was not caused by Elmiron rather it is a reflection in Elmiron patients of the generally accepted fact that men experience more cardiovascular problems than women. Each of these relationships should be interpreted with this type of caveat in mind. In addition, it should be noted that because of the use of multiple comparisons, finding four statistically significant comparisons in this type of analysis was not unreasonable even if there is not a true difference in the demographic subgroups.


Ruthanna C. Davi
Statistician, HFD-720

Concur:

Nancy Smith, Ph.D.
Division Director


1/16/96

cc:

Archival NDA#20,193
HFD-160/P. Love
HFD-160/E. Jones
HFD-160/L. Paserchia
HFD-160/S. Kummerer
HFD-160/S. Cusack
HFD-160/File Copy
HFD-344/A. Lisook
HFD-720/Chron. Copy
HFD-720/N. Smith
HFD-720/M. Welch
HFD-720/R. Davi
HFD-720/File Copy
R. Davi/x34594/WordPerfect/07/01/96
This review contains 10 pages of text and tables.

Appendix A

Table 1: Listing of Adverse Events by Age, Gender, and Race for the Open-labeled Physician Usage Study *

*This table was provided by the sponsor.

Listing of Adverse Events in Physicians Usage Study: Demographic Subset Analysis

COSTART Preferred Term	# Patients	% Patients	# 17-60 yrs	% 17-60 yrs	# 61-85 yrs	% 61-85 yrs	# Males	% Males	# Females
BODY AS A WHOLE	280	9.95	231	10.72	49	7.53	14	4.88	266
HEADACHE	82	2.92	78	3.62	4	0.61	1	0.35	81
PAIN	54	1.92	37	1.72	17	2.61	2	0.7	52
ABDOMINAL PAIN	54	1.92	41	1.9	13	2	3	1.05	51
LACK OF DRUG EFFECT	31	1.1	28	1.3	3	0.46	2	0.7	29
ASTHENA	28	1	22	1.02	6	0.92	2	0.7	26
BACK PAIN	11	0.39	10	0.46	1	0.15	0	0	11
CHEST PAIN	9	0.32	7	0.32	2	0.31	3	1.05	6
FLU SYNDROME	7	0.25	4	0.19	3	0.46	0	0	7
ALLERGIC REACTION	6	0.21	5	0.23	1	0.15	0	0	6
INDIGESTION	6	0.21	4	0.19	2	0.31	0	0	6
PB.V.C. PAIN	6	0.21	5	0.23	1	0.15	0	0	6
PHOTOSENSITIVITY REACTION	6	0.21	6	0.28	0	0	0	0	6
INFECTION	5	0.18	4	0.19	1	0.15	0	0	5
DEATH	4	0.14	1	0.05	3	0.46	1	0.35	3
FEVER	4	0.14	4	0.19	0	0	0	0	4
FACE EDEMA	3	0.11	3	0.14	0	0	0	0	3
CHILLS	2	0.07	2	0.09	0	0	0	0	2
GENERALIZED EDEMA	2	0.07	2	0.09	0	0	0	0	2
ABDOMEN ENLARGED	1	0.04	1	0.05	0	0	0	0	1
ABSCESS	1	0.04	1	0.05	0	0	0	0	1
RHEUMATOID ARTHRITIS	1	0.04	1	0.05	0	0	0	0	1
BODY ODOR	1	0.04	1	0.05	0	0	0	0	1
CARCINOMA	1	0.04	0	0	1	0.15	0	0	1
CELLULITIS	1	0.04	1	0.05	0	0	1	0.35	0
DRUG INTERACTION	1	0.04	1	0.05	0	0	0	0	1
HERNIA	1	0.04	1	0.05	0	0	0	0	1
ACCIDENTAL INJURY	1	0.04	1	0.05	0	0	0	0	1
LAB TEST ABNORMAL	1	0.04	1	0.05	0	0	0	0	1
LE SYNDROME	1	0.04	1	0.05	0	0	0	0	1
NECK RIGIDITY	1	0.04	1	0.05	0	0	0	0	1
AGGRAVATION REACTION	1	0.04	1	0.05	0	0	0	0	1
HEART AND VASCULAR SYSTEM	54	1.92	37	1.72	17	2.61	13	4.53	41
HYPERTENSION	11	0.39	6	0.28	5	0.77	2	0.7	9
MIGRAINE	10	0.36	10	0.46	0	0	1	0.35	9
TACHYCARDIA	5	0.18	4	0.19	1	0.15	0	0	5
CARDIOVASCULAR DISORDER	4	0.14	3	0.14	1	0.15	2	0.7	2
MICROCARDIAL INFARCT	4	0.14	2	0.09	2	0.31	3	1.05	1
PALITATION	3	0.11	3	0.14	0	0	0	0	3
VASCULATATION	3	0.11	2	0.09	1	0.15	0	0	3
ANGINA PECTORIS	2	0.07	1	0.05	1	0.15	1	0.35	1
HYPOTENSION	2	0.07	2	0.09	0	0	1	0.35	1
BRADYCARDIA	1	0.04	1	0.05	0	0	0	0	1
CEREBROVASCULAR ACCIDENT	1	0.04	0	0	1	0.15	1	0.35	0
CORONARY ARTERY DISORDER	1	0.04	0	0	1	0.15	1	0.35	0
VASCULAR HEADACHE	1	0.04	0	0	1	0.15	0	0	1
HEART ARREST	1	0.04	0	0	1	0.15	0	0	1
HEMORRHAGE	1	0.04	0	0	1	0.15	0	0	1
SUBARACHNOID HEMORRHAGE	1	0.04	1	0.05	0	0	0	0	1
RETINAL ARTERY OCCLUSION	1	0.04	0	0	1	0.15	0	0	1
SYNCOPE	1	0.04	1	0.05	0	0	0	0	1
SUPRAVENTRICULAR TACHYCARDIA	1	0.04	0	0	1	0.15	1	0.35	0
RETINAL VEIN THROMBOSIS	1	0.04	1	0.05	0	0	0	0	1
DEEP THROMBOPHLEBITIS	1	0.04	1	0.05	0	0	0	0	1
VASCULAR DISORDER	1	0.04	1	0.05	0	0	0	0	1
GASTROINTESTINAL SYSTEM	354	12.6	279	12.95	75	11.52	27	9.41	327
DIARRHEA	108	3.77	87	4.04	19	2.82	7	2.44	99
INDIGESTION	104	3.7	91	4.22	13	2	8	2.79	95
DYSPEPSIA	61	2.17	48	2.23	13	2	3	1.05	58
LIVER FUNCTION TESTS ABNOR	29	1.03	25	1.16	4	0.61	2	0.7	27
FLATULENCE	23	0.82	20	0.93	3	0.46	2	0.7	21
VOMITING	15	0.53	14	0.65	1	0.15	1	0.35	14
GASTROINTESTINAL DISORDER	13	0.46	11	0.51	2	0.31	0	0	13
GGT AND ALP TRANSFERRIN	10	0.36	9	0.42	1	0.15	2	0.7	8
INDIGESTION AND VOMITING	9	0.32	8	0.37	1	0.15	0	0	9
CONSTIPATION	8	0.28	3	0.14	5	0.77	1	0.35	7
MOUTH ULCERATION	8	0.28	7	0.32	1	0.15	0	0	8

DRY MOUTH	7	0.25	6	0.28	1	0.15	0	0	7
ERUCTION	6	0.21	2	0.09	4	0.61	1	0.35	5
ANOREXIA	5	0.18	2	0.09	3	0.46	0	0	5
GASTRITIS	5	0.18	3	0.14	2	0.31	1	0.35	4
OCULITIS	4	0.14	3	0.14	1	0.15	0	0	4
DYSPHAGIA	4	0.14	4	0.19	0	0	0	0	4
GUM HEMORRHAGE	4	0.14	4	0.19	0	0	0	0	4
ESOPHAGITIS	3	0.11	2	0.09	1	0.15	0	0	3
RECTAL HEMORRHAGE	3	0.11	3	0.14	0	0	0	0	3
TOOTH DISORDER	3	0.11	2	0.09	1	0.15	0	0	3
OCULOTHIASIS	2	0.07	2	0.09	0	0	0	0	2
PROCTITIS	2	0.07	1	0.05	1	0.15	1	0.35	1
STOMATITIS	2	0.07	2	0.09	0	0	0	0	2
PERIODONTAL ABSCESS	1	0.04	1	0.05	0	0	0	0	1
CHOLECYSTITIS	1	0.04	1	0.05	0	0	0	0	1
ULCERATIVE COLITIS	1	0.04	1	0.05	0	0	0	0	1
BLOODY DIARRHEA	1	0.04	1	0.05	0	0	0	0	1
TOOTH DISCOLORATION	1	0.04	0	0	1	0.15	0	0	1
GASTROENTERITIS	1	0.04	0	0	1	0.15	0	0	1
GINGIVITIS	1	0.04	1	0.05	0	0	0	0	1
GLOSSITIS	1	0.04	0	0	1	0.15	0	0	1
GASTROINTESTINAL HEMORRHAGE	1	0.04	0	0	1	0.15	0	0	1
HEPATOMA	1	0.04	0	0	1	0.15	1	0.35	0
RECTAL INCONTINENCE	1	0.04	1	0.05	0	0	0	0	1
LARGE INTESTINE PERFORATION	1	0.04	0	0	1	0.15	0	0	1
MELENA	1	0.04	0	0	1	0.15	1	0.35	0
INTESTINAL OBSTRUCTION	1	0.04	1	0.05	0	0	0	0	1
BILIARY PAIN	1	0.04	1	0.05	0	0	0	0	1
PEPTIC ULCER SYNDROME	1	0.04	1	0.05	0	0	0	0	1
INCREASED SALIVATION	1	0.04	0	0	1	0.15	1	0.35	0
TENESMUS	1	0.04	1	0.05	0	0	0	0	1
TOOTH CARIES	1	0.04	1	0.05	0	0	0	0	1
DUODENAL ULCER	1	0.04	1	0.05	0	0	0	0	1
REACTIVATED DUODENAL ULCER	1	0.04	1	0.05	0	0	1	0.35	0
STOMACH ULCER	1	0.04	0	0	1	0.15	0	0	1
STOMACH ULCER HEMORRHAGE	1	0.04	0	0	1	0.15	0	0	1
ENDOCRINE SYSTEM	6	0.21	6	0.28	0	0	0	0	6
THYROID DISORDER	2	0.07	2	0.09	0	0	0	0	2
ALDOSTERONE INCREASED	1	0.04	1	0.05	0	0	0	0	1
CUSHING SYNDROME	1	0.04	1	0.05	0	0	0	0	1
GOUT	1	0.04	1	0.05	0	0	0	0	1
PROLACTIN INCREASED	1	0.04	1	0.05	0	0	0	0	1
HEMOLYMPHATIC SYSTEM	62	2.21	45	2.09	17	2.61	6	2.09	56
ECCHYMOSIS	18	0.64	16	0.74	2	0.31	1	0.35	17
ANGINA	17	0.6	9	0.42	8	1.23	1	0.35	16
LEUKOPENIA	8	0.28	5	0.23	3	0.46	1	0.35	7
THROMBOCYTOPENIA	6	0.21	4	0.19	2	0.31	1	0.35	5
HYPOCHROMIC ANEMIA	5	0.18	5	0.23	0	0	1	0.35	4
LEUKOCYTOSIS	3	0.11	2	0.09	1	0.15	1	0.35	2
EOSINOPHILIA	2	0.07	2	0.09	0	0	1	0.35	1
LYMPHADENOPATHY	2	0.07	2	0.09	0	0	0	0	2
LYMPHOCYTOSIS	2	0.07	0	0	2	0.31	2	0.7	0
PROTHROMBIN INCREASED	2	0.07	1	0.05	1	0.15	0	0	2
MEGALOERYTHROCYTIC DISORDER	1	0.04	1	0.05	0	0	0	0	1
PETECCHIA	1	0.04	0	0	1	0.15	0	0	1
PLATELET ADHESIVENESS DECR	1	0.04	1	0.05	0	0	0	0	1
ERYTHROCYTES ABNORMAL	1	0.04	0	0	1	0.15	0	0	1
SPLENOMEGALY	1	0.04	1	0.05	0	0	0	0	1
THROMBOPLASTIN DECREASED	1	0.04	1	0.05	0	0	0	0	1
METABOLIC/NUTRITIONAL SYSTEM	68	2.42	55	2.55	13	2	8	2.79	60
WEIGHT GAIN	19	0.68	16	0.74	3	0.46	2	0.7	17
EDEMA	9	0.32	7	0.32	2	0.31	1	0.35	8
LACTIC DEHYDROGENASE INCREASED	8	0.28	6	0.28	2	0.31	1	0.35	7
SODIUM INCREASED	8	0.28	7	0.32	1	0.15	2	0.7	6
SODIUM DECREASED	7	0.25	7	0.32	0	0	4	1.39	3
WEIGHT LOSS	7	0.25	8	0.23	2	0.31	0	0	7
PERRIPHERAL EDEMA	4	0.14	2	0.09	2	0.31	0	0	4
ICTERUS	3	0.11	2	0.09	1	0.15	1	0.35	2
HYPERCHOLESTEROLEMIA	2	0.07	2	0.09	0	0	1	0.35	1
ALKALINE PHOSPHATASE INCREASED	2	0.07	1	0.05	1	0.15	0	0	2

CREATINE PHOSPHOKINASE INC	1	0.04	1	0.05	0	0	0	0	1
GENERALIZED EDEMA	1	0.04	1	0.05	0	0	0	0	1
HYPERGLYCEMIA	1	0.04	1	0.05	0	0	0	0	1
HYPERURICEMIA	1	0.04	1	0.05	0	0	0	0	1
HYPERURICEMIA	1	0.04	1	0.05	0	0	0	0	1
HYPOCHOLESTEREMIA	1	0.04	1	0.05	0	0	0	0	1
HYPOKALEMIA	1	0.04	1	0.05	0	0	0	0	1
HYPOPHOSPHATEMIA	1	0.04	1	0.05	0	0	0	0	1
*MUSCULOSKELETAL SYSTEM	32	1.14	25	1.16	7	1.08	2	0.7	30
ARTHRALGIA	17	0.6	14	0.65	3	0.46	2	0.7	15
MYALGIA	7	0.25	5	0.23	2	0.31	1	0.35	6
ARTHRITIS	3	0.11	2	0.09	1	0.15	0	0	3
ARTHROSIS	2	0.07	1	0.05	1	0.15	0	0	2
PATHOLOGICAL FRACTURE	1	0.04	1	0.05	0	0	0	0	1
LEG CRAMPS	1	0.04	1	0.05	0	0	0	0	1
TENDONOUS CONTRACTURE	1	0.04	1	0.05	0	0	0	0	1
JOINT DISORDER	1	0.04	1	0.05	0	0	0	0	1
OSTEOPOROSIS	1	0.04	1	0.05	0	0	0	0	1
TENDON DISORDER	1	0.04	1	0.05	0	0	0	0	1
TENDOSYNITIS	1	0.04	1	0.05	0	0	0	0	1
TWITCHING	1	0.04	1	0.05	0	0	0	0	1
*NERVOUS SYSTEM	99	3.52	79	3.67	20	3.07	9	3.14	90
DIZZINESS	31	1.1	25	1.16	6	1.92	4	1.38	27
PARESTHESIA	16	0.64	15	0.7	3	0.6	1	0.35	17
INSOMNIA	13	0.46	10	0.46	3	0.41	2	0.7	11
DEPRESSION	11	0.39	8	0.37	3	0.46	0	0	11
HYPERTONIA	7	0.25	5	0.23	2	0.31	1	0.35	6
NERVOUSNESS	7	0.25	5	0.23	2	0.31	1	0.35	6
SOMNOLENCE	6	0.21	6	0.28	0	0	0	0	6
CONFUSION	4	0.14	2	0.09	2	0.31	1	0.35	3
ABNORMAL DREAMS	3	0.11	2	0.09	1	0.15	0	0	3
DEPERSONALIZATION	2	0.07	2	0.09	0	0	0	0	2
TREMOR	2	0.07	1	0.05	1	0.15	0	0	2
VERTIGO	2	0.07	1	0.05	1	0.15	1	0.35	1
AGITATION	1	0.04	0	0	1	0.15	0	0	1
ANXIETY	1	0.04	1	0.05	0	0	0	0	1
INCOORDINATION	1	0.04	1	0.05	0	0	0	0	1
LEG CRAMPS	1	0.04	1	0.05	0	0	0	0	1
PSYCHOTIC DEPRESSION	1	0.04	1	0.05	0	0	0	0	1
DIPLOPIA	1	0.04	1	0.05	0	0	0	0	1
EMOTIONAL LABILITY	1	0.04	1	0.05	0	0	0	0	1
EUPHORIA	1	0.04	1	0.05	0	0	0	0	1
HYPERTENSION	1	0.04	1	0.05	0	0	0	0	1
HYSTERIA	1	0.04	1	0.05	0	0	0	0	1
MANIC REACTION	1	0.04	0	0	1	0.15	0	0	1
NEURALGIA	1	0.04	1	0.05	0	0	0	0	1
OPTIC NEURITIS	1	0.04	1	0.05	0	0	0	0	1
PERIPHERAL NEURITIS	1	0.04	1	0.05	0	0	0	0	1
NEUROPATHY	1	0.04	1	0.05	0	0	0	0	1
FACIAL PARALYSIS	1	0.04	1	0.05	0	0	0	0	1
PSYCHOSSIS	1	0.04	0	0	1	0.15	0	0	1
SCREAMING SYNDROME	1	0.04	0	0	1	0.15	0	0	1
SLEEP DISORDER	1	0.04	1	0.05	0	0	0	0	1
*RESPIRATORY SYSTEM	46	1.64	27	1.72	9	1.38	3	1.05	43
PHARYNGITIS	11	0.39	9	0.42	2	0.31	1	0.35	10
RHINITIS	10	0.36	8	0.37	2	0.31	1	0.35	9
SINUSITIS	9	0.32	9	0.42	0	0	1	0.35	8
EPISTAXIS	8	0.28	7	0.32	1	0.15	0	0	8
BRONCHITIS	6	0.21	6	0.28	0	0	1	0.35	5
DYSPINEA	5	0.18	3	0.14	2	0.31	1	0.35	4
COUGH INCREASED	3	0.11	2	0.09	1	0.15	0	0	3
ASTHMA	2	0.07	2	0.09	0	0	0	0	2
LARYNGITIS	2	0.07	2	0.09	0	0	0	0	2
CARCINOMA OF LUNG	1	0.04	0	0	1	0.15	0	0	1
PNEUMONIA	1	0.04	1	0.05	0	0	0	0	1
VOICE ALTERATION	1	0.04	0	0	1	0.15	0	0	1
*SKIN AND APPENDAGES	221	7.65	171	7.9	50	7.68	7	2.44	214
ALOPECIA	110	3.91	86	3.99	24	3.69	2	0.7	108
RASH	71	2.53	56	2.56	16	2.46	4	1.39	67
PRURITUS	19	0.68	15	0.7	4	0.61	1	0.35	18

SWEATING	11	0.39	7	0.32	4	0.61	1	0.35	10
HAIR DISORDER	5	0.18	3	0.14	2	0.31	0	0	5
URTICARIA	5	0.18	5	0.23	0	0	0	0	5
MESOCYLLIC RASH	4	0.14	3	0.14	1	0.15	0	0	4
DRY SKIN	4	0.14	3	0.14	1	0.15	0	0	4
ACNE	3	0.11	3	0.14	0	0	0	0	3
HAIR DISORDER	3	0.11	2	0.09	1	0.15	0	0	3
MACULOPAPULAR RASH	3	0.11	3	0.14	0	0	0	0	3
HIRSUZISM	2	0.07	2	0.09	0	0	0	0	2
SKIN DISCOLORATION	2	0.07	1	0.07	1	0.15	0	0	2
EXFOLIATIVE DERMATITIS	1	0.04	0	0	1	0.15	0	0	1
ECZEMA	1	0.04	1	0.05	0	0	0	0	1
HERPES ZOSTER	1	0.04	1	0.05	0	0	0	0	1
SKIN BENIGN NEOPLASM	1	0.04	0	0	1	0.15	0	0	1
PUSTULAR RASH	1	0.04	1	0.05	0	0	0	0	1
SEBORRHEA	1	0.04	0	0	1	0.15	0	0	1
SKIN DISORDER	1	0.04	1	0.05	0	0	0	0	1
TASTE SENSES	40	1.42	28	1.3	12	1.84	5	1.74	35
AMELYOSIA	6	0.21	5	0.23	1	0.15	1	0.35	5
CONJUNCTIVITIS	6	0.21	3	0.14	3	0.45	1	0.35	5
TASTE PERVERSION	5	0.18	3	0.14	2	0.31	1	0.35	4
TINNITUS	4	0.14	1	0.05	3	0.45	2	0.7	2
EAR DISORDER	3	0.11	2	0.09	1	0.15	0	0	3
LACRIMATION DISORDER	3	0.11	3	0.14	0	0	0	0	3
EYE DISORDER	2	0.07	2	0.09	0	0	0	0	2
EYE HEMORRHAGE	2	0.07	2	0.09	0	0	0	0	2
KERATOCONJUNCTIVITIS	2	0.07	1	0.05	1	0.15	0	0	2
OPTIC ATROPHY	1	0.04	1	0.05	0	0	0	0	1
CATARACT SPECTRED	1	0.04	1	0.05	0	0	0	0	1
DEAFNESS	1	0.04	1	0.05	0	0	0	0	1
RETINAL HEMORRHAGE	1	0.04	1	0.05	0	0	0	0	1
OPTIC NEURITIS	1	0.04	1	0.05	0	0	0	0	1
OTITIS EXTERNA	1	0.04	1	0.05	0	0	0	0	1
EAR PAIN	1	0.04	1	0.05	0	0	0	0	1
EYE PAIN	1	0.04	1	0.05	0	0	0	0	1
PHOTOPHOBIA	1	0.04	1	0.05	0	0	0	0	1
RETINAL DISORDER	1	0.04	0	0	1	0.15	0	0	1
TASTE LOSS	1	0.04	0	0	1	0.15	0	0	1
ABNORMAL VISION	1	0.04	1	0.05	0	0	0	0	1
VISUAL FIELD DEFECT	1	0.04	1	0.05	0	0	0	0	1
UROGENITAL SYSTEM	104	3.7	88	4.08	16	2.46	8	2.79	95
HEMATURIA	13	0.45	10	0.45	3	0.45	2	0.7	11
URINARY TRACT INFECTION	13	0.45	11	0.51	2	0.31	1	0.35	12
DYSURIA	11	0.39	7	0.32	4	0.61	0	0	11
VAINITIS	11	0.39	10	0.45	1	0.15	0	0	11
CYSTITIS	10	0.35	8	0.37	2	0.31	1	0.35	9
METRORRHAGIA	6	0.21	6	0.28	0	0	0	0	6
VAGINAL MONILIASIS	6	0.21	5	0.23	1	0.15	0	0	6
URINARY FREQUENCY	6	0.21	4	0.19	2	0.31	0	0	6
METRORRHAGIA	5	0.18	5	0.23	0	0	0	0	5
URETHRAL PAIN	4	0.14	3	0.14	1	0.15	0	0	4
URINE ABNORMALITY	4	0.14	3	0.14	1	0.15	1	0.35	3
ENDOMETRIAL DISORDER	3	0.11	3	0.14	0	0	0	0	3
MASITIS	3	0.11	3	0.14	0	0	0	0	3
MENSTRUAL DISORDER	3	0.11	3	0.14	0	0	0	0	3
BREAST CARCINOMA	2	0.07	2	0.09	0	0	0	0	2
UTERINE HEMORRHAGE	2	0.07	2	0.09	0	0	0	0	2
HYPOMENORRHEA	2	0.07	2	0.09	0	0	0	0	2
AMENORRHEA	1	0.04	1	0.05	0	0	0	0	1
BALANITIS	1	0.04	1	0.05	0	0	1	0.35	0
BLADDER CALCULUS	1	0.04	0	0	1	0.15	0	0	1
FIBROCYSTIC BREAST	1	0.04	1	0.05	0	0	0	0	1
PROSTATIC CARCINOMA	1	0.04	1	0.05	0	0	1	0.35	0
DYSMENORRHEA	1	0.04	1	0.05	0	0	0	0	1
EPIDIDYMITIS	1	0.04	1	0.05	0	0	1	0.35	0
VAGINAL HEMORRHAGE	1	0.04	1	0.05	0	0	0	0	1
KIDNEY CALCULUS	1	0.04	1	0.05	0	0	0	0	1
ACUTE KIDNEY FAILURE	1	0.04	1	0.05	0	0	0	0	1
FEMALE LACTATION	1	0.04	0	0	0	0	0	0	1
NEPHRITIS	1	0.04	1	0.05	0	0	0	0	1

NICTURA	1	004	1	005	0	0	0	0	1
PYRROCLAUSTRUM SUBPOD	1	004	1	005	0	0	0	0	1
PROSTATIC DYSORDER	1	004	1	005	0	0	1	0.35	0
PIELONEPHRITIS	1	004	1	005	0	0	0	0	1
SALPINGITIS	1	004	1	005	0	0	0	0	1
URINARY RETENTION	1	004	1	005	0	0	1	0.35	0
UTERINE FIBROIDS ENLARGED	1	004	1	005	0	0	0	0	1

→ R.C.

Memorandum of Consultation

NDA 20-193

DATE: SEP 19 1994

SPONSOR: Baker Norton Pharmaceuticals, Inc.

DRUG: Elmiron (pentosan polysulfate sodium) Capsules

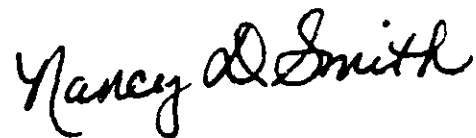
INDICATION: Interstitial cystitis.

This memorandum is in response to the suggestion that the data from the two pivotal trials submitted by Baker Norton in support of NDA 20-193 be combined into a single large trial. The Statistical Review and Evaluation of this NDA, written by Beth Turney and dated September 30, 1993, stated that from a statistical perspective the major problem with the NDA was that the two studies were not independent. In fact, three investigators participated in both studies, contributing 75% of the patients in one and 57% of the patients in the other. Additional problems included lack of a specified primary endpoint, lack of adjustment for multiple comparisons, treatment by investigator interaction, and data collection problems. However, Ms Turney concludes that she would be willing to accept the results of Study E-002 as supportive evidence of efficacy, if the results were confirmed by another trial which was completely independent of these trials, and which specified a single primary efficacy parameter or a plan for the adjustment for multiple comparisons when necessary.

There are several problems with pooling the data from the two studies. The inclusion criteria differ somewhat, as is described in Dr. Waymack's Medical Review of August 29, 1994. Dr. Waymack also notes that several of the endpoints were not quantified identically. One additional problem is that it is impossible to ascertain if some of the patients might have been involved in both trials, since three investigators participated in both trials. It is always a controversial decision to combine the data from different studies, and I think it would clearly be a mistake in this case.

This reviewer also has a problem with a meta analysis of the two studies, again because of the duplication of investigators and possible duplication of patients. The minor differences between the trials would probably not matter for a meta-analysis, but the lack of a pre-specified primary endpoint, and consequent multiple comparison adjustment requirements, would likely still result in many of the endpoints lacking statistical significance.

This reviewer feels that the sponsor should be encouraged to do one large, multi-center study, involving none of the investigators who participated in either of the earlier studies. They should specify a single primary endpoint or a plan for multiple comparison adjustments, and should carefully consider how the data for these endpoints will be collected. The sample size should be large enough to assure power to detect a clinically significant difference. Strategies should be included which would encourage patients to remain in the study until the end of the three-month treatment period, and to return for a final evaluation at the scheduled time even if they have discontinued the study prior to three months. The protocol for this study, including case-report forms and a statistical analysis plan, should be submitted to the FDA for review, and the study should not be initiated until the agency has reviewed and commented on the protocol.



Nancy D. Smith, Ph.D.
Mathematical Statistician

cc

Orig. NDA 20-193

HFD-160/Dr. Waymack, Dr. Love

HFD-160/Dr. Cheever, Ms Rhee

HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]

HFD-713/Dr. Smith

Chron.

Memorandum of Consultation

Date: January 3, 1994

To: Dr. Patricia Love, HFD-160

From: *N Smith*
Dr. Nancy Smith and Dr. Ralph Harkins, HFD-713

Re: NDA 20-193, Elmiron

I have reviewed the statistical responses in the Medical Review of Elmiron and have the following comments. The numbers refer to the numbers in the Medical Review and in the sponsor's submission:

Response 1: It is the PMA position that such a correction in p-values should be made. Our Statistical Reviewer, Review dated September 30, 1993, promoted this position.

Response 1a: Our statistical reviewer's report of September 30 supports the Medical Officer's conclusions.

Response 1b: The Statistical Review of September 30, 1993, agrees that the intent-to-treat for Study E001 was correct. For Study E002, three subjects were not carried forward. However, when this was done by our reviewer it did not change the conclusions.

Response 1d: The subgroup analyses were post-hoc and exploratory in nature. They are useful for hypothesis generation, but should not be used to make claims. Subgroup analyses, when specified a priori, require adjustment for multiple comparisons. This is unrealistic for post-hoc subgroup analyses since the potential number of subgroups is infinite.

Response 2: The table indicates an increasing response over the three month period. This is not quite the same as claiming that '6-8 weeks of Elmiron therapy may be required to achieve a beneficial result'.

Response 3: These problems were discussed extensively in the earlier Statistical Review, and the conclusions were identical to those expressed by the Medical Review.

Response 4: Because of the sponsor's unwillingness to perform a withdrawal study, we agree with the Medical Reviewer that an additional well-controlled pivotal trial as discussed in Response 3 should be required.

cc:

Orig. NDA 20-193

HFD-160/Dr. Waymack

HFD-160/Ms Rhee

HFD-713/Dr. Harkins *Ralph Harkins*

HFD-713/Dr. Smith

Chron.

STATISTICAL REVIEW AND EVALUATION

NDA: 20-193 SEP 30 1993

Applicant: Baker-Norton Pharmaceuticals, Inc.

Name of Drug: pentosan polysulfate sodium (ELMIRON[®])

Documents Reviewed: original NDA volumes 1.10, 1.11, 1.13, and 1.17 dated 6-11-91; previous statistical reviews dated 11-10-88 and 11-8-91; the not approvable letter dated 1-27-93; amendment volumes 1-3 of the applicant's response to the not approvable letter, dated 7-7-93

Indication: treatment of interstitial cystitis

Medical Officer: Patricia Love, M.D., HFD-160

I. INTRODUCTION

This review pertains to the applicant's response to clinical deficiencies 1 (including sections a and b) and 2 cited in the not approvable letter dated 1-27-93. A copy of the not approvable letter is included in Appendix III.

II. EVALUATION

A. METHODS

Protocols E-001 and E-002 were multicenter, randomized (1:1 within each center), double-blind, parallel group, placebo controlled studies designed to evaluate the efficacy and safety of 100 mg Elmiron[®] t.i.d. in the treatment of interstitial cystitis. Except where noted, the protocols are similar.

Patients were followed for 3 months, where clinic visits occurred at baseline and after 3 months of treatment. Patients performed self evaluations at home after 1 month and 2 months of treatment. These protocols also had open label treatment and follow-up periods of 1 (E-002) to 2 (E-001) years.

The applicant's per protocol analysis included all randomized patients who met the entrance criteria for parameters associated with the status of their interstitial cystitis at the time of entry. In addition to the entrance criteria, each patient was required to have at least one follow up evaluation after treatment initiation. An endpoint analysis, where the last observation was carried forward for patients who discontinued early, was emphasized. Patients who had missing overall evaluations at termination were excluded from the analysis.

The applicant's intent-to-treat analysis included all randomized patients. An endpoint analysis, where the last observation was carried forward for patients who discontinued early, was

emphasized. In the event there was no treatment evaluation, the baseline value was brought forward. If there were no overall evaluations at termination, the outcome was considered unchanged.

In the re-analysis of the data, the applicant presented the following six variables as the primary efficacy parameters, which are the focus of this review:

1. Decrease in bladder pain based on the change in rating scale from baseline to endpoint.
2. Improvement in bladder pain based on patient overall assessment (global).
3. Decrease in urgency based on the change in rating scale from baseline to endpoint.
4. Improvement in urgency based on patient overall assessment (global).
5. Overall improvement based on patient evaluation (global).
6. Overall improvement based on investigator evaluation (global).

In the applicant's re-analysis, the global evaluations (bladder pain, urgency, overall improvement) were assigned to a six point scale, where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement. The applicant considered a score of 2 or greater as a successful response.

The bladder pain and urgency analog scales had discrete ratings from 0 to 5, where 0 = none, 1 = mild, 3 = moderate, and 5 = severe. Ratings of 2 and 4 were possible, but these responses did not have an associated word description. The applicant considered a decrease from baseline of 1 unit or more as a successful response.

The applicant performed three types of analyses on the success rate of each parameter:

1. Assessment of treatment effect: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.
2. Assessment of investigator effect: general association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.
3. Assessment of treatment by investigator interaction: Breslow-Day test.

A significance level of 0.05 was used for all tests.

This reviewer analyzed the treatment effect within each site using Fisher's exact test, and assessed the potential treatment by investigator interaction using the method outlined by DerSimonian and Laird [Controlled Clinical Trials (1986) 7:177-188].

In response to the request to identify subgroups in which the drug is effective, the applicant performed a wide array of exploratory subgroup analyses using contingency table and logistic regression methods. The studies were combined for the subgroup analyses.

REVIEWER COMMENTS: It is not clear which of the primary efficacy parameters the applicant considers most important. In protocol E-001, the applicant did not assign a hierarchy to the primary efficacy parameters or provide an interpretation criteria in the event that the results fail to agree on all parameters. In protocol E-002, a 3 parameter hierarchy was suggested:

1. Overall improvement based on patient evaluation.

NDA 28-193

5 OF 7

2. Decrease in bladder pain based on the change in rating scale from baseline to endpoint.
3. Overall improvement based on investigator evaluation.

If approval could be granted based on any one of the applicant's six primary parameters, then issue of multiple comparisons needs to be addressed. It is the opinion of this reviewer that the significance level of each independent test must be adjusted in order to maintain the integrity of the overall significance level of the trial. It is the opinion of this reviewer that there are 4 independent parameters: bladder pain, urgency, overall patient evaluation, overall investigator evaluation.

After reviewing the CRF from protocol E-001, it is difficult to determine how the data collected on the patient follow up questionnaire regarding the global evaluations of bladder pain and overall improvement could be translated to a six point scale where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement. The wording of the questions did not allow for responses of "worse" or "unchanged". The data integrity of these measures in study E-001 is questionable. A copy of the patient questionnaire from protocol E-001 is displayed in Appendix III.

This reviewer considers an interaction to be significant at the 0.15 level.

In order to estimate sample size for study E-002, an unplanned interim analysis was performed during study E-001. The applicant contends that since the results of the interim analysis were not divulged to any study participant and did not change the performance of the study, an adjustment to the overall significance level is not necessary. However, it is the opinion of this reviewer that an adjustment should have been made in this situation. In the analysis of the primary efficacy parameters of study E-001, this reviewer used an adjusted overall significance level of 0.048 as proposed by the method of O'Brien and Fleming [Biometrics 1979;35:549-556].

Three investigators (Hanno, Parsons, and Sant), participated in both protocols E-001 and E-002. These investigators made up 75% (82/110) of the patients enrolled in protocol E-001 and 57% (85/148) of the patients enrolled in protocol E-002. Clearly, studies E-001 and E-002 are not independent.

The applicant failed to present a longitudinal analysis of the treatment effect over time. This type of analysis would be necessary to support the labelling claim relief of symptoms may not be experienced until after 6 to 8 weeks therapy.

It is the opinion of this reviewer that the results from unplanned exploratory subgroup analyses must be interpreted with extreme caution, especially in the situation where a significant treatment effect is not observed in the overall study population. The applicant's exploratory subgroup analyses are not addressed in this review.

B. PROTOCOL E-001 RESULTS

A total of 110 patients were enrolled across 5 investigative sites. Fifty-four patients were randomized to Elmiron[®], and 56 patients were randomized to placebo. Enrollment by investigator ranged from 12 to 31.

Three (6%) Elmiron[®] patients and 9 (16%) placebo patients discontinued prior to the 3 month evaluation. The treatment difference was marginally significant ($p = 0.077$).

All patients were included in the intent-to-treat (ITT) analysis. With respect to baseline characteristics, there were no statistically significant treatment imbalances. There was significant investigator variability with respect to several baseline characteristics; however, it is the opinion of this reviewer that the investigator variability in these parameters did not impact study conclusions.

Thirty (56%) Elmiron[®] patients and 28 (50%) placebo patients were included in the per-protocol (PP) analysis. With respect to the percentage of patients included in the per-protocol analysis, there was no statistically significant treatment difference within investigator or combined across investigators. However, there was significant variability among investigators with respect to the percentage of patients included in the per-protocol analysis, which ranged from 25% (3/12) for investigator 2 to 81% (22/27) for investigator 3 ($p = 0.001$). Investigators 2 and 5 were pooled as a single investigator in the per-protocol analysis. With respect to baseline characteristics, there were no statistically significant treatment imbalances. There was significant investigator variability with respect to several baseline characteristics; however, it is the opinion of this reviewer that the investigator variability in these parameters did not impact study conclusions.

Results for each efficacy parameter are presented by investigator and combined across investigators in Tables 1-6 of Appendix I. The results for each parameter are as follows:

1. Patient global evaluation of overall improvement at endpoint: The direction of the treatment effect, in favor of Elmiron[®], was similar in both the PP and ITT populations; however, the treatment effect was statistically significant only in the ITT population. A significant treatment by investigator interaction was observed in the ITT population. The interaction appears to be due to investigator 1, the largest center, and the center where the treatment effect was highest in magnitude. The treatment effect and interaction are no longer significant when investigator 1 is excluded from the analysis. ✓

2. Decrease in bladder pain based on the change in rating scale from baseline to endpoint: The direction of the treatment effect, in favor of Elmiron[®], was similar in both the PP and ITT populations; however, the treatment effect was statistically significant only in the ITT population. A significant treatment by investigator interaction was observed in the PP population. Since the direction of treatment effect is highly inconsistent among investigators, the significant interaction cannot be attributed to one particular investigator.

3. Investigator global evaluation of overall improvement at endpoint: A statistically significant treatment effect, in favor of Elmiron[®], was observed in both the PP and ITT populations.

4. Decrease in urgency based on the change in rating scale from baseline to endpoint: The direction of the treatment effect, in favor of placebo, was similar in both the PP and ITT populations; however, the treatment effect was not statistically significant in either population. A significant treatment by investigator interaction was observed in the PP population. Since the direction of treatment effect is highly inconsistent among investigators, the significant interaction cannot be attributed to one particular investigator.

5. Patient global evaluation of bladder pain at endpoint: The direction of the treatment effect, in favor of Elmiron[®], was similar in both the PP and ITT populations; however, the treatment effect was not statistically significant in either population.

6. Patient global evaluation of urgency at endpoint: The direction of the treatment effect, in favor of Elmiron[®], was similar in both the PP and ITT populations; however, the treatment effect was not statistically significant in either population. A statistically significant investigator effect was observed in the ITT population. The investigator effect appears to be due to investigator 1, which had the highest degree of response in both treatment groups. The investigator effect is no longer significant when investigator 1 is excluded.

REVIEWER COMMENTS: As discussed in section IIA above, the patient global evaluations of bladder pain and overall improvement have data collection problems which, in the opinion of this reviewer, render them unreliable for the assessment of efficacy.

Of the 4 remaining primary efficacy parameters, statistical significance at the 0.048 level was attained for only 1 parameter in the PP population (investigator overall improvement) and 2 parameters in the ITT population (change in bladder pain rating and investigator overall improvement). For all parameters, the direction of the treatment effect was consistent across both populations. In 3 of the 4 parameters, the treatment effect favored Elmiron[®].

The issue of multiple comparisons has not been addressed in the applicant's analysis. If a Bonferroni correction for multiple comparisons is applied for the number of independent tests performed, the corrected significance level would be $0.048/3 = 0.016$. At this level of significance, only one parameter in the ITT population (change in bladder pain rating) has a statistically significant treatment effect.

Agreement between the two urgency parameters would be expected; however, this result was not observed. The direction of the treatment effect favored placebo for the change in urgency rating, and Elmiron[®] for overall improvement in urgency.

It is the opinion of this reviewer that a serious treatment by investigator interaction problem is not present in this trial. The observed responses cannot be consistently attributed to a single investigator.

The major flaw of this trial is that it is not independent of study E-002. The two small centers which did not participate in study E-002 have a combined enrollment of 14 patients per treatment arm, and cannot stand alone in an efficacy analysis.

This reviewer concludes that study E-001 fails to provide substantial evidence in support of the applicant's claim that 3 months of 100 mg Elmiron[®] t.i.d. is efficacious in the treatment of interstitial cystitis.

C. PROTOCOL E-002 RESULTS

A total of 151 patients were enrolled across 7 investigative sites. Seventy-six patients were randomized to Elmiron[®], and 75 patients were randomized to placebo. Three patients (2 Elmiron[®] and 1 placebo) never received treatment and were excluded from all analyses; thus

74 patients per treatment arm were enrolled and treated. The number of patients enrolled and treated by investigator ranged from 8 to 33.

Ten patients (14%) in each treatment group discontinued prior to the 3 month evaluation.

All patients were included in the intent-to-treat (ITT) analysis. There was a statistically significant treatment imbalance with respect to sex distribution, where placebo had significantly more males than Elmiron[®] (7% versus 0%, $p=0.018$). There was significant investigator variability with respect to several baseline characteristics. It is the opinion of this reviewer that the treatment and investigator imbalances in these parameters did not impact study conclusions.

Thirty-eight (49%) Elmiron[®] patients and 47 (64%) placebo patients were included in the per-protocol (PP) analysis. With respect to the percentage of patients included in the per-protocol analysis, there was a marginally statistically significant treatment imbalance ($p=0.077$). This imbalance is primarily due to investigator 2, who included 19% (3/16) Elmiron[®] patients compared to 53% (9/17) placebo patients ($p=0.071$). There was marginally significant variability among investigators with respect to the percentage of patients included in the per-protocol analysis, which ranged from 36% (12/33) for investigator 2 to 86% (12/14) for investigator 6 ($p=0.065$). Investigators 3 and 5 were pooled as a single investigator in the per-protocol analysis. There were statistically significant treatment imbalances with respect to mean bladder capacity and mean 24 hour frequency, where placebo had a significantly smaller bladder capacity and significantly greater 24 hour frequency than Elmiron[®] (bladder capacity: 605 cc versus 688 cc, $p=0.038$; 24 hour frequency: 17.4 versus 13.2, $p=0.005$). There was significant investigator variability with respect to several baseline characteristics. It is the opinion of this reviewer that the treatment and investigator imbalances in these parameters did not impact study conclusions.

Results for each efficacy parameter are presented by investigator and combined across investigators in Tables 1-6 of Appendix II. The results for each parameter are as follows:

1. Patient global evaluation of overall improvement at endpoint: The direction of the treatment effect, in favor of Elmiron[®], was similar in both the PP and ITT populations; however, the treatment effect was statistically significant only in the ITT population. The treatment by investigator interaction was significant in both populations, and the investigator effect was significant in the ITT population. The significant investigator effect and interactions appear to be due to investigator 1. When this investigator is excluded from the PP and ITT analyses, the treatment effect, investigator effect and interactions are no longer significant.

2. Decrease in bladder pain based on the change in rating scale from baseline to endpoint: The direction of the treatment effect, in favor of Elmiron[®], was similar in both the PP and ITT populations; however, the treatment effect was not statistically significant in either population. A significant treatment by investigator interaction was observed in the ITT population. The interaction appears to be due to investigator 3. The interaction is longer significant when this investigator is excluded.

3. Investigator global evaluation of overall improvement at endpoint: A statistically significant treatment effect, in favor of Elmiron[®], was observed in both the PP and ITT populations. The

treatment by investigator interaction was significant in both populations, and the investigator effect was significant in the ITT population. In the PP population, the significant interaction appears to be due to investigator 1. When this investigator is excluded from the PP analysis, the treatment effect and interaction are no longer significant. In the ITT population, the significant investigator effect and interaction appear to be due to investigators 1 and 7. When these investigators are excluded from the ITT analysis, the treatment effect, investigator effect, and interaction are no longer significant.

4. Decrease in urgency based on the change in rating scale from baseline to endpoint: A statistically significant treatment effect, in favor of Elmiron[®], was observed in both the PP and ITT populations. The treatment by investigator interaction was also significant in both populations. The significant interactions appear to be due to investigator 1. When this investigator is excluded from the PP and ITT analyses, the treatment effects and interactions are no longer significant.

5. Patient global evaluation of bladder pain at endpoint: A statistically significant treatment effect, in favor of Elmiron[®], was observed in both the PP and ITT populations. The treatment by investigator interaction was significant in both populations, and the investigator effect was significant in the ITT population. In both populations, the significant interaction appears to be due to investigator 1. When this investigator is excluded from the PP and ITT analyses, the treatment effects and interactions are no longer significant. In the ITT population, the significant investigator effect appears to be due to investigators 1 and 7. When these investigators are excluded from the ITT analysis, the treatment effect, investigator effect, and interaction are no longer significant.

6. Patient global evaluation of urgency at endpoint: The direction of the treatment effect, in favor of Elmiron[®], was similar in both the PP and ITT populations; however, the treatment effect was statistically significant only in the ITT population. The treatment by investigator interaction was significant in both populations. The significant interactions appear to be due to investigator 1. When this investigator is excluded from the PP and ITT analyses, the treatment effects and interactions are no longer significant.

REVIEWER COMMENTS: Of the 6 primary efficacy parameters, statistical significance at the 0.050 level was attained for 4 parameters in the PP population (investigator overall improvement, change in urgency rating, overall improvements in bladder pain and urgency), and 4 parameters in the ITT population (patient and investigator overall improvement, change in urgency rating, and overall improvement in bladder pain). For all parameters, the direction of the treatment effect favored Elmiron[®], and was consistent across both populations.

The issue of multiple comparisons has not been addressed in the applicant's analysis. If a Bonferroni correction for multiple comparisons is applied for the number of independent tests performed, the corrected significance level would be $0.05/4 = 0.013$. At this level of significance, a significant treatment effect was observed in 2 parameters in the PP population (investigator overall improvement and change in urgency rating) and 2 parameters in the ITT population (investigator overall improvement and overall improvement in bladder pain).

A serious treatment by investigator interaction problem is present in this trial. The significant treatment effects observed in this trial are highly influenced by investigator 1 (Parsons).

Investigator 1 was one of the larger centers, and in most cases had the greatest magnitude of treatment effect in favor of Elmiron[®]. In general, the interaction appeared to be due to investigator differences in the magnitude of the treatment effect rather than the direction of the treatment effect; however, since the trial was made up of relatively small centers, it is difficult to clearly determine the mode of interaction. Results for all parameters when investigator 1 is excluded are displayed in Table 7 of Appendix II. When investigator 1 is excluded, the direction of the treatment effect still favors Elmiron[®] for all parameters; however, none of the treatment effects are statistically significant.

This reviewer concludes that study E-002 fails to provide substantial evidence in support of the applicant's claim that 3 months of 100 mg Elmiron[®] t.i.d. is efficacious in the treatment of interstitial cystitis.

III. SUMMARY AND CONCLUSIONS **(Which May be Conveyed to the Applicant)**

Statistical evaluation of comparative efficacy was based on 6 parameters designated by the applicant as "primary": patient global evaluation of overall improvement at endpoint, decrease in bladder pain based on the change in rating scale from baseline to endpoint, investigator global evaluation of overall improvement at endpoint, decrease in urgency based on the change in rating scale from baseline to endpoint, patient global evaluation of overall improvement in bladder pain, and patient global evaluation of overall improvement in urgency.

In the re-analysis of the data, the applicant failed to address the issue of multiple comparisons. If approval could be granted based on any one of the applicant's six primary parameters, it is the opinion of this reviewer that the significance level of each independent test must be adjusted in order to maintain the integrity of the overall significance level of the trial. There are a variety of methodologies for multiple comparisons adjustment; this reviewer applied a Bonferroni correction. Due to the small size of the per-protocol populations, this reviewer considered the intent-to-treat population as the primary efficacy population. In both studies for all parameters, the direction of the treatment effect was similar in the per-protocol and intent-to-treat populations. All comparisons were made against placebo.

1. Study E-001: The patient global evaluations of bladder pain and overall improvement have data collection problems which, in the opinion of this reviewer, render them unreliable for the assessment of efficacy.

At the uncorrected significance level of 0.048, Elmiron[®] had a significantly higher proportion of patients with at least a 1 unit decrease in bladder pain based on the change in rating scale from baseline to endpoint, and a significantly higher proportion of patients with at a score of 2 or greater for the investigator global evaluation of overall improvement at endpoint. At the Bonferroni corrected significance level of $0.048/3 = 0.016$, Elmiron[®] had a significantly higher proportion of patients with at least a 1 unit decrease in bladder pain based on the change in rating scale from baseline to endpoint.

The major flaw of this trial is that it is not independent of study E-002. Three investigators (Hanno, Parsons, and Sant), participated in both protocols E-001 and E-002. These investigators made up 75% (82/110) of the patients enrolled in protocol E-001 and 57% (85/148) of the patients enrolled in protocol E-002. The two small centers which participated in study E-001 and did not participate in study E-002 have a combined enrollment of 14 patients per treatment arm, and cannot stand alone in an efficacy analysis.

2. Study E-002: At the uncorrected significance level of 0.05, Elmiron[®] had a significantly higher proportion of patients with at least a 1 unit decrease in urgency based on the change in rating scale from baseline to endpoint, and a significantly higher proportion of patients with a score of 2 or greater for the investigator global evaluation of overall improvement at endpoint, patient global evaluation of overall improvement at endpoint, and patient global evaluation of overall improvement in bladder pain at endpoint. At the Bonferroni corrected significance level of $0.05/4 = 0.013$, Elmiron[®] had a significantly higher proportion of patients with a score of 2 or greater for the investigator global evaluation of overall improvement at endpoint and for the patient global evaluation of overall improvement in bladder pain.

This trial has a serious treatment by investigator interaction problem, where the significant treatment effects observed are highly influenced by investigator 1 (Parsons). When investigator 1 is excluded, the direction of the treatment effect still favors Elmiron[®]; however, the treatment effects are no longer statistically significant at the 0.05 level.

REVIEWER CONCLUSIONS: From a statistical perspective, study independence is the primary issue of concern. The applicant has failed to provide two independent, adequate and well controlled trials which substantiate the claim that 3 months of 100 mg Elmiron[®] t.i.d. is efficacious in the treatment of interstitial cystitis.

This reviewer would be willing to accept the results of study E-002 as supportive evidence for the applicant's efficacy claim. However, a pivotal trial which uses investigators who did not participate in E-001 or E-002, which specifies in the protocol a single primary efficacy parameter or a plan for multiple comparisons adjustment, and which demonstrates that 3 months of 100 mg Elmiron[®] t.i.d. is efficacious in the treatment of interstitial cystitis is needed.

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HFD-713/Harkins

HFD-713/Turney ←

HFD-344/Lisook

Chron.

This review contains 10 pages and 3 appendices.

APPENDIX I: Tables for Study E-001

TABLE 1: Study E-001							
Success Rate for Patient Global Evaluation of Overall Improvement at Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Hanno	Elmiron placebo	7	3 (43)	>0.999	15	8 (53)	0.023
		4	1 (25)		16	2 (13)	
2 [*] Mulholland	Elmiron placebo	4	0 (0)	-	6	0 (0)	>0.999
		4	0 (0)		6	1 (17)	
3 Parsons	Elmiron placebo	11	4 (36)	0.311	13	4 (31)	0.165
		10	1 (10)		14	1 (7)	
4 Sant	Elmiron placebo	7	1 (14)	>0.999	12	1 (8)	>0.999
		9	1 (11)		12	2 (17)	
5 [*] Staskin	Elmiron placebo				8	2 (25)	>0.999
					8	1 (13)	
all	Elmiron placebo	29	8 (28)	0.177	54	15 (28)	0.042
		27	3 (11)		56	7 (13)	
investigator p-value ³		0.264			0.284		
interaction test p-values ⁴		0.769 (0.628)			0.147 (0.042)		

¹ A score of 2 or greater on the global scale (relative to baseline) where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

* In the per-protocol analysis, investigators 2 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 2: 2 Elmiron, 1 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 2.

TABLE 2: Study E-001							
Success Rate for Decrease in Bladder Pain Based on the Change in Rating Scale From Baseline to Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Hanno	Elmiron placebo	8	3 (38)	0.545	15	6 (40)	0.716
		4	3 (75)		16	5 (31)	
2* Mulholland	Elmiron placebo	3	1 (33)	>0.999	6	3 (50)	0.545
		3	1 (33)		6	1 (17)	
3 Parsons	Elmiron placebo	11	5 (45)	0.361	13	6 (46)	0.103
		11	2 (18)		14	2 (14)	
4 Jant	Elmiron placebo	7	5 (71)	0.126	12	6 (50)	0.400
		9	2 (22)		12	3 (25)	
5* Staskin	Elmiron [®] placebo				7	3 (43)	0.077
					8	0 (0)	
all	Elmiron placebo	29	14 (48)	0.187	53	22 (42)	0.005
		27	8 (27)		56	13 (23)	
investigator p-value ³		0.776			0.819		
interaction test p-values ⁴		0.134 (0.089)			0.540 (0.735)		

¹ A decrease of 1 unit on a scale of 0 to 5, where 0 = none, 1 = mild, 3 = moderate, and 5 = severe.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

* In the per-protocol analysis, investigators 2 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 2: 2 Elmiron, 1 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 2.

® One Elmiron patient at this center did not have a baseline rating and was excluded from the ITT analysis.

TABLE 3: Study E-001							
Success Rate for Investigator Global Evaluation of Overall Improvement at Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Hanno	Elmiron placebo	8	3 (38)	>0.999	15	6 (40)	0.113
		4	1 (25)		16	2 (13)	
2 [*] Mulholland	Elmiron placebo	4	0 (0)	-	6	0 (0)	>0.999
		4	0 (0)		6	1 (17)	
3 Parsons	Elmiron placebo	11	4 (36)	0.311	13	4 (31)	0.165
		11	1 (9)		14	1 (7)	
4 Sant	Elmiron placebo	7	2 (29)	0.175	12	2 (17)	>0.999
		9	0 (0)		12	1 (8)	
5 [*] Staskin	Elmiron placebo				8	2 (25)	>0.999
					8	1 (13)	
all	Elmiron placebo	30	9 (30)	0.042	54	14 (26)	0.039
		28	2 (7)		56	6 (11)	
investigator p-value ³		0.343			0.617		
interaction test p-values ⁴		0.524 (0.876)			0.471 (0.258)		

¹ A score of 2 or greater on the global scale (relative to baseline) where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

* In the per-protocol analysis, investigators 2 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 2: 2 Elmiron, 1 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 2.

TABLE 4: Study E-001							
Success Rate for Decrease in Urgency Based on the Change in Rating Scale From Baseline to Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Hanno	Elmiron placebo	8	2 (25)	0.222	15	5 (33)	>0.999
		4	3 (75)		16	5 (31)	
2* Mulholland	Elmiron placebo	3	0 (0)	0.400	6	0 (0)	0.455
		3	2 (67)		6	2 (33)	
3 Parsons	Elmiron placebo	11	4 (36)	>0.999	13	4 (31)	>0.999
		11	3 (27)		14	4 (29)	
4 Sant	Elmiron placebo	7	5 (71)	0.358	12	8 (67)	0.414
		9	4 (44)		12	5 (42)	
5* Staskin	Elmiron® placebo				7	3 (43)	0.315
					8	6 (75)	
all	Elmiron placebo	29	11 (38)	0.675	53	20 (38)	0.875
		27	12 (44)		56	22 (39)	
investigator p-value ³		0.511			0.059		
interaction test p-values ⁴		0.074 (0.019)			0.238 (0.192)		

¹ A decrease of 1 unit on a scale of 0 to 5, where 0 = none, 1 = mild, 3 = moderate, and 5 = severe.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

* In the per-protocol analysis, investigators 2 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 2: 2 Elmiron, 1 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 2.

® One Elmiron patient at this center did not have a baseline rating and was excluded from the ITT analysis.

TABLE 5: Study E-001							
Success Rate for Patient Global Evaluation of Overall Improvement in Bladder Pain at Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Hanno	Elmiron placebo	8 4	3 (38) 2 (50)	>0.999	15 16	6 (40) 3 (19)	0.252
2 [*] Mulholland	Elmiron placebo	4 4	0 (0) 0 (0)	-	6 6	0 (0) 0 (0)	-
3 Parsons	Elmiron placebo	11 11	4 (36) 1 (9)	0.311	13 14	4 (31) 1 (7)	0.165
4 Sant	Elmiron placebo	7 9	3 (43) 1 (11)	0.262	12 12	3 (25) 2 (17)	>0.999
5. Staskin	Elmiron placebo				8 8	1 (13) 1 (13)	>0.999
all	Elmiron placebo	30 28	10 (33) 4 (14)	0.127	54 56	14 (26) 7 (13)	0.068
investigator p-value ³		0.267			0.244		
interaction test p-values ⁴		0.308 (0.449)			0.781 (0.687)		

¹ A score of 2 or greater on the global scale (relative to baseline) where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

*In the per-protocol analysis, investigators 2 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 2: 2 Elmiron, 1 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 2.

TABLE 6: Study E-001
Success Rate for Patient Global Evaluation of Overall Improvement in Urgency at
Endpoint by Investigator and Combined Across Investigators
For the Applicant's Per-Protocol and Intent-to-Treat Populations

investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Hanno	Elmiron placebo	8	3 (38)	>0.999	15	7 (47)	0.135
		4	2 (50)		16	3 (19)	
2 [*] Mulholland	Elmiron placebo	4	0 (0)	-	6	0 (0)	-
		4	0 (0)		6	0 (0)	
3 Parsons	Elmiron placebo	11	3 (27)	0.586	13	3 (23)	0.326
		10	1 (10)		14	1 (7)	
4 Sant	Elmiron placebo	7	1 (14)	0.438	12	1 (8)	>0.999
		9	0 (0)		12	1 (8)	
5 [*] Staskin	Elmiron placebo				8	1 (13)	>0.999
					8	1 (13)	
all	Elmiron placebo	30	7 (23)	0.398	54	12 (22)	0.087
		27	3 (11)		56	6 (11)	
investigator p-value ³		0.077			0.048		
interaction test p-values ⁴		0.393 (0.676)			0.757 (0.464)		

¹ A score of 2 or greater on the global scale (relative to baseline) where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

^{*} In the per-protocol analysis, investigators 2 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 2: 2 Elmiron, 1 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 2.

APPENDIX II: Tables for Study E-002

TABLE 1: Study E-002							
Success Rate for Patient Global Evaluation of Overall Improvement at Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Parsons	Elmiron placebo	10	7 (70)	0.011	15	10 (67)	0.008
		6	0 (0)		14	2 (14)	
2 Hanno	Elmiron placebo	3	0 (0)	>0.999	16	1 (6)	>0.999
		9	1 (11)		17	1 (6)	
3 [*] Benson	Elmiron placebo	3	0 (0)	0.500	5	2 (40)	0.444
		6	2 (33)		4	0 (0)	
4 Childs	Elmiron placebo	10	4 (40)	0.659	16	5 (31)	>0.999
		11	3 (27)		16	5 (31)	
5 [*] Frye	Elmiron placebo				4	1 (25)	>0.999
					4	2 (20)	
6 Webster	Elmiron placebo	5	1 (20)	>0.999	6	1 (17)	>0.999
		7	1 (14)		8	2 (25)	
7 Sant	Elmiron placebo	3	1 (33)	0.333	12	4 (33)	0.093
		6	0 (0)		11	0 (0)	
all	Elmiron placebo	34	13 (38)	0.084	74	24 (32)	0.022
		45	7 (16)		74	12 (16)	
investigator p-value ³		0.439			0.045		
interaction test p-values ⁴		0.120 (<0.001)			0.092 (0.016)		

¹ A score of 2 or greater on the global scale (relative to baseline) where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

* In the per-protocol analysis, investigators 3 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 3: 1 Elmiron, 3 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 3.

TABLE 2: Study E-002							
Success Rate for Decrease in Bladder Pain Based on the Change in Rating Scale From Baseline to Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Parsons	Elmiron placebo	10 6	6 (60) 2 (33)	0.608	15 14	9 (60) 5 (36)	0.272
2 Hanno	Elmiron placebo	3 9	3 (100) 5 (56)	0.491	16 17	9 (56) 9 (53)	>0.999
3 [*] Benson	Elmiron placebo	3 6	2 (67) 2 (33)	0.524	5 4	4 (80) 0 (0)	0.048
4 Childs	Elmiron placebo	10 11	6 (60) 8 (73)	0.659	16 16	9 (56) 11 (69)	0.716
5 [*] Frye	Elmiron placebo				4 4	2 (50) 2 (50)	>0.999
6 Webster	Elmiron placebo	5 7	4 (80) 3 (43)	0.293	6 8	5 (83) 3 (38)	0.138
7 Sant	Elmiron placebo	4 7	3 (75) 3 (43)	0.545	12 11	5 (42) 4 (36)	>0.999
all	Elmiron placebo	35 46	24 (69) 23 (50)	0.075	74 74	43 (58) 34 (46)	0.127
investigator p-value ³		0.741			0.710		
interaction test p-values ⁴		0.530 (0.406)			0.184 (0.006)		

¹ A decrease of 1 unit on a scale of 0 to 5, where 0 = none, 1 = mild, 3 = moderate, and 5 = severe.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

^{*} In the per-protocol analysis, investigators 3 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 3: 1 Elmiron, 3 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 3.

TABLE 3: Study E-002							
Success Rate for Investigator Global Evaluation of Overall Improvement at Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Parsons	Elmiron placebo	10	8 (80)	0.007	15	11 (73)	0.003
		6	0 (0)		14	2 (14)	
2 Hanno	Elmiron placebo	3	0 (0)	>0.999	16	1 (6)	>0.999
		9	1 (11)		17	1 (6)	
3 [*] Benson	Elmiron placebo	3	0 (0)	0.500	5	1 (20)	>0.999
		6	2 (33)		4	0 (0)	
4 Childs	Elmiron placebo	10	4 (40)	0.361	16	5 (31)	>0.999
		11	2 (18)		16	4 (25)	
5 [*] Frye	Elmiron placebo				4	1 (25)	>0.999
					4	2 (50)	
6 Webster	Elmiron placebo	5	1 (20)	>0.999	6	1 (17)	>0.999
		7	1 (14)		8	2 (25)	
7 Sant	Elmiron placebo	4	2 (50)	0.109	12	7 (58)	0.005
		7	0 (0)		11	0 (0)	
all	Elmiron placebo	35	15 (43)	0.013	74	27 (36)	0.003
		46	6 (13)		74	11 (15)	
investigator p-value ³		0.433			0.024		
interaction test p-values ⁴		0.056 (<0.001)			0.040 (0.001)		

¹ A score of 2 or greater on the global scale (relative to baseline) where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

^{*} In the per-protocol analysis, investigators 3 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 3: 1 Elmiron, 3 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 3.

TABLE 4: Study E-002
Success Rate for Decrease in Urgency Based on the Change in Rating Scale From Baseline to Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations

investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Parsons	Elmiron placebo	10 6	10 (100) 1 (17)	0.001	15 14	12 (80) 4 (29)	0.009
2 Hanno	Elmiron placebo	3 9	2 (67) 5 (56)	>0.999	16 17	6 (38) 7 (41)	>0.999
3 [*] Benson	Elmiron placebo	3 6	2 (67) 2 (33)	0.524	5 4	4 (80) 0 (0)	0.048
4 Childs	Elmiron placebo	10 11	5 (50) 6 (55)	>0.999	16 16	8 (50) 8 (50)	>0.999
5 [*] Frye	Elmiron placebo				4 4	2 (50) 3 (75)	>0.999
6 Webster	Elmiron placebo	5 7	3 (60) 2 (29)	0.558	6 8	4 (67) 3 (38)	0.592
7 Sant	Elmiron placebo	4 7	3 (75) 3 (43)	0.545	12 11	6 (50) 4 (36)	0.680
all	Elmiron placebo	35 46	25 (71) 19 (41)	0.012	74 74	42 (57) 29 (39)	0.035
investigator p-value ³		0.841			0.858		
interaction test p-values ⁴		0.121 (0.022)			0.076 (0.003)		

¹ A decrease of 1 unit on a scale of 0 to 5, where 0 = none, 1 = mild, 3 = moderate, and 5 = severe.
² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.
³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.
⁴ Breslow-Day test (DerSimonian and Laird test).
^{*} In the per-protocol analysis, investigators 3 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 3: 1 Elmiron, 3 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 3.

TABLE 5: Study E-002							
Success Rate for Patient Global Evaluation of Overall Improvement in Bladder Pain at Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations							
investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Parsons	Elmiron placebo	10 6	7 (70) 0 (0)	0.011	15 14	11 (73) 2 (14)	0.003
2 Hanno	Elmiron placebo	3 9	0 (0) 1 (11)	>0.999	16 17	1 (6) 1 (6)	>0.999
3 [*] Benson	Elmiron placebo	3 6	1 (33) 2 (33)	>0.999	5 4	2 (40) 0 (0)	0.444
4 Childs	Elmiron placebo	10 11	4 (40) 4 (36)	>0.999	16 16	5 (31) 6 (38)	>0.999
5 [*] Frye	Elmiron placebo				4 4	2 (50) 2 (50)	>0.999
6 Webster	Elmiron placebo	5 7	2 (40) 1 (14)	0.523	6 8	2 (33) 2 (25)	>0.999
7 Sant	Elmiron placebo	3 6	2 (67) 0 (0)	0.083	12 11	5 (42) 0 (0)	0.037
all	Elmiron placebo	34 45	16 (47) 8 (18)	0.019	74 74	28 (38) 13 (18)	0.005
investigator p-value ³		0.645			0.016		
interaction test p-values ⁴		0.130 (<0.001)			0.072 (0.005)		

¹ A score of 2 or greater on the global scale (relative to baseline) where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

^{*} In the per-protocol analysis, investigators 3 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 3: 1 Elmiron, 3 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 3.

TABLE 6: Study E-002

Success Rate for Patient Global Evaluation of Overall Improvement in Urgency at Endpoint by Investigator and Combined Across Investigators For the Applicant's Per-Protocol and Intent-to-Treat Populations

investigator	treatment	per-protocol			intent-to-treat		
		total n	success ¹ n (%)	p-value ²	total n	success ¹ n (%)	p-value ²
1 Parsons	Elmiron placebo	10	6 (60)	0.034	15	9 (60)	0.021
		6	0 (0)		14	2 (14)	
2 Hanno	Elmiron placebo	3	0 (0)	>0.999	16	1 (6)	>0.999
		9	1 (11)		17	2 (12)	
3 [*] Benson	Elmiron placebo	2	1 (50)	0.464	5	2 (40)	0.444
		6	1 (17)		4	0 (0)	
4 Childs	Elmiron placebo	10	4 (40)	0.659	16	5 (31)	>0.999
		11	3 (27)		16	5 (31)	
5 [*] Frye	Elmiron placebo				4	1 (25)	>0.999
					4	1 (25)	
5 Webster	Elmiron placebo	5	1 (20)	>0.999	6	1 (17)	>0.999
		7	1 (14)		8	2 (25)	
6 Sant	Elmiron placebo	3	1 (33)	>0.999	12	3 (25)	0.590
		6	1 (17)		11	1 (9)	
all	Elmiron placebo	33	13 (39)	0.050	74	22 (30)	0.088
		45	7 (16)		74	13 (18)	
investigator p-value ³		0.729			0.196		
interaction test p-values ⁴		0.535 (0.011)			0.294 (0.094)		

¹ A score of 2 or greater on the global scale (relative to baseline) where -1 = worse, 0 = unchanged, 1 = 25% improvement, 2 = 50% improvement, 3 = 75% improvement, and 4 = 100% improvement.

² For each investigator: Fisher's exact test. For all investigators combined: general association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

³ General association Cochran-Mantel-Haenszel chi-square test of investigator by response controlling for treatment.

⁴ Breslow-Day test (DerSimonian and Laird test).

* In the per-protocol analysis, investigators 3 and 5 were combined due to small sample sizes. The per-protocol sample sizes were as follows: investigator 3: 1 Elmiron, 3 placebo; investigator 5: 2 Elmiron, 3 placebo. Results for this combined center are displayed under investigator 3.

TABLE 7: Study E-002
Success Rate for Primary Parameters When Investigator 1 (Parsons) is Excluded
For the Applicant's Per-Protocol and Intent-to-Treat Populations

parameter	treatment	per-protocol			intent-to-treat		
		total n	success n (%)	p-value ¹	total n	success n (%)	p-value ¹
patient overall imp.	Elmiron placebo	24	6 (25)	0.710	59	14 (24)	0.346
		39	7 (18)		60	10 (17)	
change in bladder pain	Elmiron placebo	25	18 (72)	0.136	59	34 (58)	0.287
		40	21 (53)		60	29 (48)	
investigator overall imp.	Elmiron placebo	25	7 (28)	0.298	59	16 (27)	0.107
		40	6 (15)		60	9 (15)	
change in urgency	Elmiron placebo	25	15 (60)	0.227	59	30 (51)	0.319
		40	18 (45)		60	25 (42)	
overall imp. bladder pain	Elmiron placebo	24	9 (38)	0.240	59	17 (29)	0.171
		39	8 (21)		60	11 (18)	
overall imp. urgency	Elmiron placebo	23	7 (30)	0.376	59	13 (22)	0.629
		39	7 (18)		60	11 (18)	

¹ General association Cochran-Mantel-Haenszel chi-square test of treatment by response controlling for investigator.

**RANDOMIZED PROSPECTIVE STUDY OF EFFICACY OF SODIUM PENTOSANPOLYSULFATE
IN THE TREATMENT OF INTERSTITIAL CYSTITIS**

FOLLOW-UP QUESTIONNAIRE

NAME: _____

DATE _____

PATIENT NO. _____

(Please circle the word that best answers the question)

1. Do you notice any difference in pressure to urinate? Yes No

2. If you answered "yes" to Question #1, is the pressure to urinate Better Worse

3. If you answered "better", which best describes the improvement?
 - a) slight improvement (25%)
 - b) moderate improvement (50%)
 - c) great improvement (75%)
 - d) symptoms are gone (100%)

4. How often do you urinate? _____

5. Do you still have pain with urination? Yes No

6. If the pain is better, is it Yes No
 - a) slight improvement (25%)
 - b) moderate improvement (50%)
 - c) great improvement (75%)
 - d) pain gone (100%)

7. Do you get up at night to void? Yes No
If "yes", how often? _____

8. Do you think you get a better night's sleep now than before the treatment? Yes No

9. Do you feel that you are improved overall since the treatment started? Yes No

10. If you feel improved, which answer best describes the improvement over the past month?
 - a) slight improvement (25%)
 - b) moderate improvement (50%)
 - c) great improvement (75%)
 - d) complete cure (100%)

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STATISTICAL REVIEW AND EVALUATION

NOV 8 1991

NDA#: 20-193

APPLICANT: Baker Cummins Pharmaceuticals, Inc.

NAME OF DRUG: Elmiron (pentosan polysulfate sodium)

INDICATION: Treatment of Interstitial Cystitis

DOCUMENTS REVIEWED: Volumes 1.13 - 1.20 dated 6-11-91

This review pertains to two placebo controlled, three month studies of Elmiron for the treatment of patients with interstitial cystitis.

The medical officer for this submission is C. Rodriguez, M.D. (HFD-160).

I. BACKGROUND

There were extensive discussions between Dr. Richard Stein (HFD-713) and the company's consulting statistician, Dr. J. Trout, about how these studies would be analyzed. These discussions were summarized in Dr. Stein's statistical review dated 10-10-88 (IND

II. STUDY DESCRIPTION AND METHOD OF ANALYSES

These were multicenter, parallel group, placebo controlled 3 month studies for the amelioration of symptoms in patients with documented interstitial cystitis.

The primary efficacy variables were patient and investigator overall evaluation, bladder pain and urgency. This review will focus only on these measures.

Efficacy data recorded at baseline and each monthly visit included pain (0 - none to 5 - severe) and urgency (0 - none to 5 - severe). These variables were also obtained at the last clinic visit (endpoint) if the patient dropped out early.

At the last clinic visit, patients rated their bladder pain, urgency and overall change (which included bladder pain, urgency, enjoyment of sexual intercourse, nocturia and sleep at night) using a scale [worse, no better (0%), slightly improved (25%), moderately improved (50%), greatly improved (75%), symptom(s) gone (100%)]. The investigator gave an overall evaluation of improvement using a scale.

1. worse
2. no change
3. fair: about 25% improvement in one or more symptoms
4. good: about 50% improvement in two or more symptoms
5. very good: about 75% improvement in two or more symptoms
6. excellent: about 100% improvement in essentially all symptoms

The sponsor's statistical consultant (Dr. J. Trout) indicated that the primary analysis of efficacy variables would be done using 2 X 2 tables using Fisher's exact test for individual investigators and Cochran-Mantel-Haenszel test on the combined data. The two stratification factors are treatment (Elmiron vs placebo) and better vs not better. The 4 primary analyses were stated to be patient overall evaluation of improvement, investigator overall evaluation of improvement, change in analogue bladder pain scale from baseline and change in analogue urgency scale from baseline.

II RESULTS

A. STUDY E001

There were 110 patients (54 Elmiron, 56 placebo) who entered the trial. The treatment groups were comparable at baseline in demographic variables and medical history variables assessing the patients' interstitial cystitis. The treatment groups were also comparable in mean pain and urgency analogue scores at baseline.

Nine patients withdrew early on placebo compared to only 3 on Elmiron. This difference in dropout rates was only nearly significant ($P=0.08$). Seven of the nine placebo dropouts were patients with severe interstitial cystitis. The difference in dropout rates among severe patients is borderline significant ($P=.05$).

Table 20 presents the results of the analysis of percentages of patients indicating that they were better for pain and urgency and overall. [The analysis of change in rating scale was stated to be the primary efficacy analysis for pain and urgency. The analysis of pain and pressure based on patient's final examination are secondary analyses.] Table 20 also includes the analysis of investigator overall evaluation.

Significant differences between treatments was seen only for patient and investigator overall evaluation. Although the Breslow-Day test for homogeneity of odds ratios was not significant for patient ($P=0.147$) or investigator ($P=.471$) overall evaluation analyses, the major contribution to the significance of the overall evaluation analyses is attributable to the results from site 1 (Dr. P. Hanno). [The results for patient overall evaluation were significant for this site alone ($P=.023$, Fisher's exact test).]

B. STUDY E002

There were 148 patients (74 in each treatment group) who received drug during the trial. Three additional patients entered the trial but never received drug. The treatment groups were comparable at baseline in demographic variables and medical history variables assessing the patient's interstitial cystitis. The treatment groups were also comparable in mean pain and urgency analogue scores at baseline.

Nineteen patients (9 Elmiron and 10 placebo) withdrew prior to completing of the double blind phase.

Table 20 presents the results of the analyses of percentages of patients indicating that they were better for pain and urgency and overall. [The analysis of change in rating scale was stated to be the primary efficacy analysis for pain and urgency. The analysis of pain and pressure based on patient's final examination are secondary analyses.] Table 20 also presents the results of the investigator's overall evaluation.

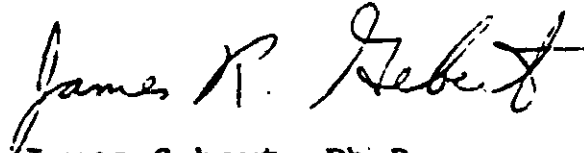
Significant differences between treatments were seen in patient and investigator overall evaluation and urgency - based on change in rating scale. There was also a significant difference in pain - based on patient's final examination, however, the analysis of pain - based on change in rating scale, which the sponsor's statistician stated would be the primary analysis, was not significant. Significant ($P < .10$) treatment by investigator interaction was detected by the Breslow-Day test. Highly significant treatment differences favoring Elmiron ($P < .01$) was found for patient and investigator overall evaluation, and urgency-based on change in rating scale in Center 1 (Dr. C. Lowell Parsons). The results of investigator overall assessment were significant ($P < .005$) also in Center 7 (Dr. Grannum R. Sant). If the data without that of Dr. C. Lowell Parsons' center are analyzed using Fisher's exact test, the results are not significant for urgency - based on change in rating scale ($P = .340$), patient overall evaluation ($P = .369$) or investigator overall evaluation ($P = .120$).

III. REVIEWER'S COMMENTS (May be sent to the Sponsor)

The evidence of efficacy of Elmiron for the treatment of interstitial cystitis is very weak. Of the four primary efficacy variables (patient overall, investigator overall, pain-based on change in rating scale and urgency-based on change in rating scale) only patient and investigator overall were significant ($P = .04$) in Study E001. (These measures would be expected to be highly correlated.) Three of the four variables (patient and

investigator overall evaluation and urgency - based on change in rating scale) were significant in Study E002. In each study there is one influential center (Dr. Hanno in Study E001 and Dr. Parsons in Study E002) that was the main contributor to the significant results seen.

If the influential center is excluded in study E002, none of the primary efficacy variables show statistical significance. Using Fisher's Exact Test, the significance values in Study E002 are $P=0.435$ for pain-based on change in rating scale, $P=0.340$ for urgency-based on change in rating scale, $P=0.369$ for overall patient evaluation, and $P=0.120$ for overall physician evaluation. If the influential center is excluded from study E001, three of the four primary efficacy variables are not significant. Using Fisher's Exact Test, the significance values are $P=0.644$ for urgency-based on change in rating scale, $P=0.546$ for overall patient evaluation, and $P=0.225$ for overall physician evaluation. The significance value for pain-based on change in rating scale is significant now ($P=0.05$) where it was not significant ($P=0.12$ using the sponsor's analyses) when this center was included.



James Gebert, Ph.D.
Mathematical Statistician, HFD-713

Concur: Dr. Nevius *JEN 11-4-91*
Dr. Dubey *6-11-7-91*

cc:
Orig. NDA 20-193
HFD-160
HFD-160/Dr. Rodriguez
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File 1.3.2. NDA]
HFD-713/Group 2 File
HFD-713/Dr. Gebert
Chron.

J. GEBERT/MEG/ELMIRON.STA/WP51/10-31-91

TABLE 20
OVERALL EVALUATION SUMMARY
STUDY E001

Response: Pain-Based on Change In Rating Scale⁽¹⁾

Treatment Group		Site					Combined	Treatment Group Comparison (p-value)
		1	2	3	4	5		
Elmiron	Better	6	1	6	6	3	22 (46%)	0.12
	Not Better	7	5	7	4	3	26 (54%)	
Placebo	Better	5	3	2	3	0	13 (29%)	
	Not Better	4	3	10	8	7	32 (71%)	

Response: Pain-Based on Patient's Final Examination⁽¹⁾

Elmiron	Better	6	0	4	3	1	14 (27%)	0.11
	Not Better	8	6	9	8	6	37 (73%)	
Placebo	Better	3	0	1	2	1	7 (14%)	
	Not Better	9	6	12	9	7	43 (86%)	

Response: Urgency-Based on Change In Rating Scale

Elmiron	Better	5	0	4	8	3	20 (39%)	0.51
	Not Better	9	6	9	3	4	31 (61%)	
Placebo	Better	5	3	4	5	6	23 (46%)	
	Not Better	7	3	9	7	1	27 (54%)	

Response: Pressure Based on Patient's Final Evaluation

Elmiron	Better	7	0	3	1	1	12 (22%)	0.09
	Not Better	8	6	10	11	7	42 (78%)	
Placebo	Better	3	0	1	1	1	6 (11%)	
	Not Better	13	6	13	11	7	50 (89%)	

Response: Overall Patient Evaluation

Elmiron	Better	8	0	4	1	2	15 (28%)	0.04
	Not Better	7	6	9	11	6	39 (72%)	
Placebo	Better	2	1	1	2	1	7 (13%)	
	Not Better	14	5	13	10	7	49 (87%)	

(1) Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis.

TABLE 20 (CONT'D)

*STUDY E001*Response: Overall Investigator Evaluation

<u>Treatment Group</u>		<u>Site</u>					<u>Combined</u>	<u>Treatment Group Comparison (p-value)</u>
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>		
Elmiron	Better	6	0	4	2	2	14 (26%)	0.04
	Not Better	9	6	9	10	6	40 (74%)	
Placebo	Better	2	1	1	1	1	6 (11%)	
	Not Better	14	5	13	11	7	50 (89%)	

TABLE 20

OVERALL EVALUATION SUMMARY
 SUMMARY OF PERCENT OF PATIENTS IMPROVED
 STUDY E002

Response: Pain-Based on Change in Rating Scale⁽¹⁾

Treatment Group	Outcome	Site							Combined	Treatment Group Comparison (p-value)
		1	2	3	4	5	6	7		
Elmiron	Better	9	9	4	9	2	5	5	43 (63%) 25 (37%)	0.15
	Not Better	5	5	1	5	2	1	6		
Placebo	Better	5	9	0	11	2	3	4	34 (52%) 32 (48%)	
	Not Better	7	6	3	4	1	5	6		

Response: Pain Based on Patient's Final Examination

Elmiron	Better	11	1	2	5	2	2	5	28 (38%) 46 (62%)	0.009
	Not Better	4	15	3	11	2	4	7		
Placebo	Better	2	1	0	6	2	2	0	13 (18%) 59 (82%)	
	Not Better	11	16	4	10	1	6	11		

Response: Urgency-Based on Change in Rating Scale

Elmiron	Better	12	6	4	8	2	4	6	42 (52%) 26 (38%)	0.03
	Not Better	2	8	1	6	2	2	5		
Placebo	Better	4	7	0	8	3	3	4	29 (43%) 39 (57%)	
	Not Better	9	8	3	7	1	5	6		

(1) Patients whose rating of pain at baseline (visit 0) was zero are excluded from this analysis.

TABLE 20 (CONT'D)

STUDY E002

Response: Urgency-Based on Patient's Final Evaluation

Treatment Group	Outcome	Site							Combined	Treatment Group Comparison (p-value)
		1	2	3	4	5	6	7		

Elmiron	Better	9	1	2	5	1	1	3	22(30%)	0.09
	Not Better	6	15	3	11	3	5	9	52(70%)	

Placebo	Better	2	2	0	5	1	2	1	13(18%)	0.02
	Not Better	12	15	4	11	3	6	10	61(82%)	

Response: Overall Patient Evaluation

Elmiron	Better	10	1	2	5	1	1	4	24(32%)	0.02
	Not Better	5	15	1	11	3	5	8	50(68%)	

Placebo	Better	7	1	0	5	2	2	0	12(16%)	0.003
	Not Better	12	16	4	11	2	6	11	62(84%)	

Response: Overall Investigator Evaluation

Elmiron	Better	11	1	1	5	1	1	7	27(36%)	0.003
	Not Better	4	15	4	11	3	5	5	47(64%)	

Placebo	Better	2	1	0	6	2	2	0	11(15%)	0.003
	Not Better	12	16	4	12	2	6	11	63(85%)	

Chem

Division of Medical Imaging, Surgical and Dental Drug Products
Review of Chemistry, Manufacturing, and Controls.

filed
at Sack

SEP 10 1995

NDA #: 20-193

REVIEWER: Patricia Stewart

CHEMISTRY REVIEW #: 6

DATE REVIEWED: 12/05/95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-19-91	06-19-91	07-02-91
AMENDMENT	12-10-92	12-11-92	12-14-92
AMENDMENT (BC)	07/20/93	07/22/93	07/27/93
AMENDMENT (AC)	02/11/94	02/14/94	02/22/94
AMENDMENT (BC)	05/22/95	05/23/95	05/31/95
AMENDMENT (AC)	10/30/95	10/31/95	11/14/95

NAME & ADDRESS OF APPLICANT: Baker Norton Pharmaceutical
8800 N.W. 36th Street
Miami, Florida 33178-2404
Contact: Jane Hsiao, Ph.D.
(305) 590-2235

DRUG PRODUCT NAME

Proprietary: Elmiron
Nonproprietary/Established/USAN: Pentosan Polysulfate Sodium
Code Name/#: SP-54, PZ-68, PPS, USAN Z-41
Chem.Type/Ther.Class: 1 C

PHARMACOLOGICAL CATEGORY/INDICATION: Non-steroidal anti-inflammatory agent for the treatment of interstitial cystitis

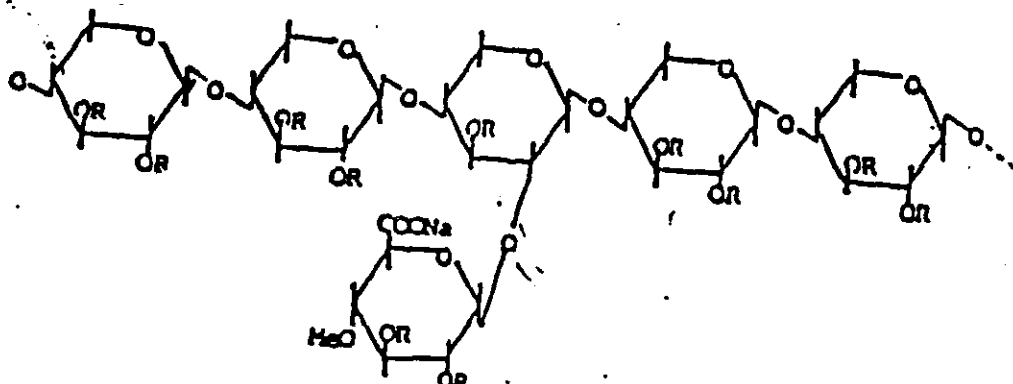
DOSAGE FORM: Capsule
STRENGTHS: 100 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

β-D-Xylan, (1-4), 2,3-bis(hydrogen sulfate), sodium salt

Empirical Formula: $[C_5H_8O_4(SO_3Na)]_n$ where $n = 11$

Molecular Weight: 3676 average



The basic unit of pentosan polysulfate sodium (PPS) is comprised of one uronic acid substituent for every ten xylose units, and most of the hydroxyls are substituted with sodium sulfate groups. The total formula of such a unit is thought (ideal model) to be $C_{57}H_{48}O_{109}S_{21}Na_{21}$, the relative molecular weight of such a unit is 3676; hence an average monomer has a molecular weight of 333.74 (3676/11). Therefore, the theoretical number of sugar units (as xylose) in an average PPS chain is estimated to be in the neighborhood of 11-12 which is in agreement with the structural formula of a xylose disaccharide with repeating units of 3 to 6. The data submitted by _____ in the DMF have demonstrated consistency in the production of PPS from 1979 to date. There are no differences in the average molecular weight based on gel chromatography.

Supporting Documents:

DMF

DMF

DMF (Baker Norton Pharmaceuticals)---- Manufacture of drug product

DMF

DMF

DMF

DMF

Related Documents:

IND

Consults:

Establishment Evaluation Request - sent 1/11/93 and 12/30/93
Environmental Assessment - Forwarded to Dr. Phil Vincent
Pharmacology - Approvable with labeling changes 12/20/91

Remarks:

Elmiron was granted an Orphan Drug designation for the treatment of interstitial cystitis 8/7/85. The clinical development of Elmiron was sponsored formerly by _____ under IND _____ Sponsorship was transferred to

_____ to Baker Norton Pharmaceuticals, Inc. October 1992. Elmiron has been provided to over 1,274 interstitial cystitis patients on request by their physicians since 1986.

CONCLUSIONS & RECOMMENDATIONS:

This application may be approved from a chemistry standpoint.

Orig. NDA 20-193
HFD-160/Division File
HFD-160/DIR/Love
HFD-830/DIR/Sheinin
HFD-160/Chem/Stewart
HFD-160/Pharm/See
HFD-160/CSO/McCort

Patricia Stewart
Review Chemist/ HFD-160
December 5, 1995

Esheini
12-10-95

Division of Medical Imaging, Surgical and Dental Drug Products
Review of Chemistry, Manufacturing, and Controls

OCT 11 1995

NDA #: 20-193

REVIEWER: Patricia Stewart

CHEMISTRY REVIEW #: 5

DATE REVIEWED: 9/12/95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-19-91	06-19-91	07-02-91
AMENDMENT	12-10-92	12-11-92	12-14-92
AMENDMENT (BC)	07/20/93	07/22/93	07/27/93
AMENDMENT (AC)	02/11/94	02/14/94	02/22/94
AMENDMENT (BC)	05/22/95	05/23/95	05/31/95

NAME & ADDRESS OF APPLICANT: Baker Norton Pharmaceutical
8800 N.W. 36th Street
Miami, Florida 33178-2404
Contact: Jane Hsiao, Ph.D.
(305) 590-2235

DRUG PRODUCT NAME

<u>Proprietary:</u>	Elmiron
<u>Nonproprietary/Established/USAN:</u>	Pentosan Polysulfate Sodium
<u>Code Name/#:</u>	SP-54, PZ-68, PPS, USAN Z-41
<u>Chem.Type/Ther.Class:</u>	1 C

PHARMACOLOGICAL CATEGORY/INDICATION: Non-steroidal anti-inflammatory agent for the treatment of interstitial cystitis

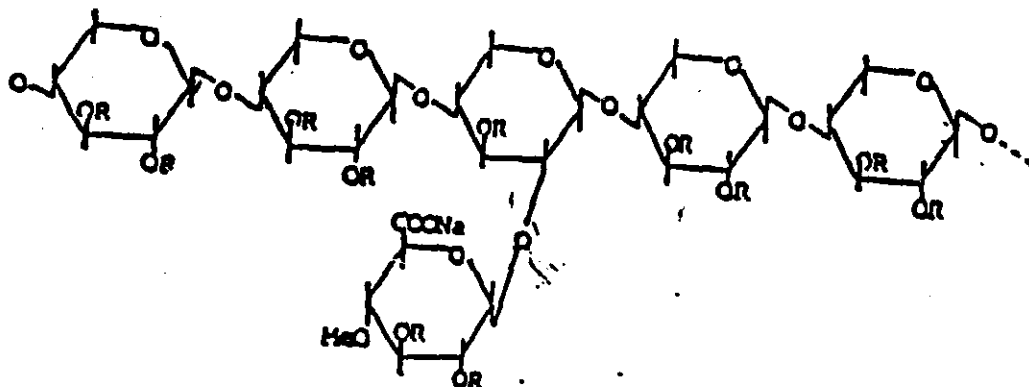
<u>DOSAGE FORM:</u>	Capsule
<u>STRENGTHS:</u>	100 mg
<u>ROUTE OF ADMINISTRATION:</u>	Oral
<u>DISPENSED:</u>	☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

β -D-Xylan, (1-4), 2,3-bis(hydrogen sulfate), sodium salt

Empirical Formula: $[C_5H_7O_4(SO_3Na)]_n$ where $n = 11$

Molecular Weight: 3676 average



The basic unit of pentosan polysulfate sodium (PPS) is comprised of one uronic acid substituent for every ten xylose units, and most of the hydroxyls are substituted with sodium sulfate groups. The total formula of such a unit is thought (ideal model) to be $C_{11}H_{18}O_{22}S_2Na_2$, the relative molecular weight of such a unit is 3676; hence an average monomer has a molecular weight of 333.74 (3676/11). Therefore, the theoretical number of sugar units (as xylose) in an average PPS chain is estimated to be in the neighborhood of 11-12 which is in agreement with the structural formula of a xylose disaccharide with repeating units of 3 to 6. The data submitted by _____ in the DMF have demonstrated consistency in the production of PPS from 1979 to date. There are no differences in the average molecular weight based on gel chromatography.

Supporting Documents:

DMF

DMF

DMF (Baker Norton Pharmaceuticals)---- Manufacture of drug product

DMF

DMF

DMF

DMF

Related Documents:

IND

Consults:

Establishment Evaluation Request - sent 1/11/93 and 12/30/93
 Environmental Assessment - Forwarded to Dr. Phil Vincent
 Pharmacology - Approvable with labeling changes 12/20/91

Remarks:

Elmiron was granted an Orphan Drug designation for the treatment of interstitial cystitis 8/7/85. The clinical development of Elmiron was sponsored formerly by _____ under IND _____ Sponsorship was transferred to

_____ to Baker Norton Pharmaceuticals, Inc. October 1992. Elmiron has been provided to over 1,274 interstitial cystitis patients on request by their physicians since 1986.

CONCLUSIONS & RECOMMENDATIONS:

This application is approvable from a chemistry standpoint. The comments in the Draft of Chemist's Part should be forwarded to the applicant.

Patricia Stewart
Review Chemist/ HFD-160
October 6, 1995

cc:
Orig. NDA 20-193
HFD-160/Division File
HFD-160/DIR/Love
HFD-160/Chem/Stewart
HFD-160/Pharm/See
HFD-161/CSO/Rhee

C. B. [Signature]
10-11-95

APR 15 1994

Division of Medical Imaging, Surgical and Dental Drug Products
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-193

REVIEWER: Patricia Stewart

CHEMISTRY REVIEW #: 4

DATE REVIEWED: 4/13/94

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-19-91	06-19-91	07-02-91
AMENDMENT	12-10-92	12-11-92	12-14-92
AMENDMENT (BC)	07/20/93	07/22/93	07/27/93
AMENDMENT (AC)	02/11/94	02/14/94	02/22/94

NAME & ADDRESS OF APPLICANT: Baker Norton Pharmaceutical
8800 N.W. 36th Street
Miami, Florida 33178-2404
Contact: Jane Hsiao, Ph.D.
(305) 590-2235

DRUG PRODUCT NAME

<u>Proprietary:</u>	Elmiron
<u>Nonproprietary/Established/USAN:</u>	Pentosan Polysulfate Sodium
<u>Code Name/#:</u>	SP-54, PZ-68, PPS, USAN 2-41
<u>Chem.Type/Ther.Class:</u>	1 C

PHARMACOLOGICAL CATEGORY/INDICATION: Non-steroidal anti-inflammatory agent for the treatment of interstitial cystitis

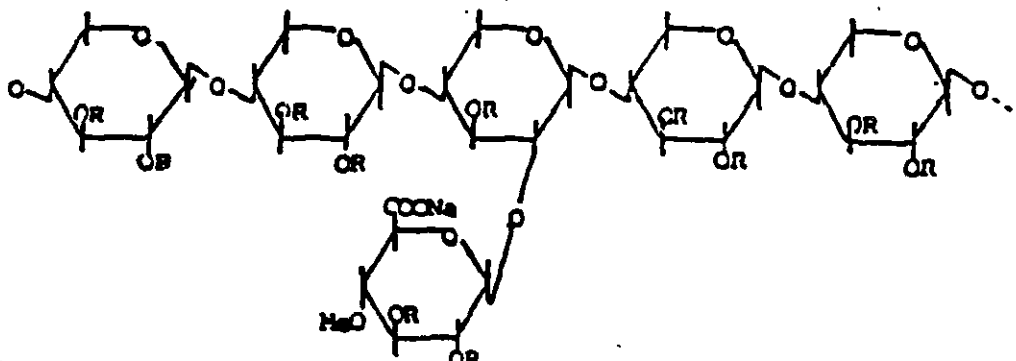
<u>DOSAGE FORM:</u>	Capsule
<u>STRENGTHS:</u>	100 mg
<u>ROUTE OF ADMINISTRATION:</u>	Oral
<u>DISPENSED:</u>	☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

β-D-Xylan, (1-4), 2,3-bis(hydrogen sulfate), sodium salt

Empirical Formula: $[C_5H_6O_4(SO_3Na)]_n$ where $n = 11$

Molecular Weight: 3676 average



The basic unit of pentosan polysulfate sodium (PPS) is comprised of one uronic acid substituent for every ten xylose units, and most of the hydroxyls are substituted with sodium sulfate groups. The total formula of such a unit is thought (ideal model) to be $C_{57}H_{48}O_{109}S_{21}Na_{22}$, the relative molecular weight of such a unit is 3676; hence an average monomer has a molecular weight of 333.74 (3676/11). Therefore, the theoretical number of sugar units (as xylose) in an average PPS chain is estimated to be in the neighborhood of 11-12 which is in agreement with the structural formula of a xylose disaccharide with repeating units of 3 to 6. The data submitted by _____ in the DMF have demonstrated consistency in the production of PPS from 1979 to date. There are no differences in the average molecular weight based on gel chromatography.

Supporting Documents:

DMF

DMF

DMF (Baker Norton Pharmaceuticals)----- Manufacture of drug product

DMF

DMF

DMF

DMF

Related Documents:

IND

Consults:

Establishment Evaluation Request - sent 1/11/93 and 12/30/93
Environmental Assessment - Forwarded to Dr. Phil Vincent
Pharmacology - Approvable with labeling changes 12/20/91

Remarks:

Elmiron was granted an Orphan Drug designation for the treatment of interstitial cystitis 8/7/85. The clinical development of Elmiron was sponsored formerly by _____ under IND _____ Sponsorship was transferred to

_____ to Baker Norton Pharmaceuticals, Inc. October 1992. Elmiron has been provided to over 1,274 interstitial cystitis patients on request by their physicians since 1986.

CONCLUSIONS & RECOMMENDATIONS:

There are still a few chemistry problems that should be resolved before final approval.

Patricia Stewart

Review Chemist/ HFD-160

cc:
Orig. NDA 20-193
HFD-160/Division File
HFD-160/DIR/Love
HFD-160/Chem/Stewart
HFD-160/Pharm/See
HFD-161/CSO/Rhee

EP Shein
4-15-94

Addendum to Chemistry Review #4
NDA 20-193
Elmiron (pentosan polysulfate sodium)

The draft Chemistry comments that were communicated to the sponsor on June 30, 1992, were satisfactorily answered by the amendment dated December 10, 1992. This amendment was a completely new CMC section allowing for the manufacture of the drug product at the Miami facility. While it did not specifically answer each question, they presented sufficient information to respond satisfactorily to the deficiencies. The outstanding issues were adequately addressed by the Chemistry Review #4 dated April 14, 1994.

Patricia Stewart 2/12/96

Patricia Stewart
Reviewing Chemist

Eldon E. Leutzinger 2/12/96

Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-160

CC Original NDA 20-193
HFD-160 Div. File
HFD-160 Cusack / Leutzinger
HFD-510 Stewart

Division of Medical Imaging, Surgical and Dental Drug Products
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-193

001 21 1993

CHEMISTRY REVIEW #: 3

DATE REVIEWED: 9/8/93

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-19-91	06-19-91	07-02-91
AMENDMENT	12-10-92	12-11-92	12-14-92
AMENDMENT (BC)	07/20/93	07/22/93	07/27/93

NAME & ADDRESS OF APPLICANT:

Baker Norton Pharmaceutical
8800 N.W. 36th Street
Miami, Florida 33178-2404
Contact: Edward Gubish, Ph.D.
(303) 590-2617

DRUG PRODUCT NAME

<u>Proprietary:</u>	Elmiron
<u>Nonproprietary/Established/USAN:</u>	Pentosan Polysulfate Sodium
<u>Code Name/#:</u>	SP-54, PZ-68, PPS, USAN Z-41
<u>Chem.Type/Ther.Class:</u>	1 C

PHARMACOLOGICAL CATEGORY/INDICATION: Non-steroidal anti-inflammatory agent for the treatment of interstitial cystitis -

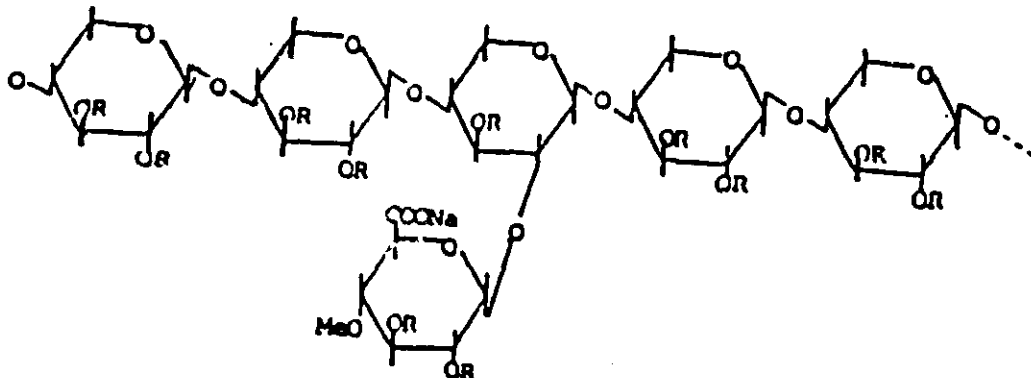
<u>DOSAGE FORM:</u>	Capsule
<u>STRENGTHS:</u>	100 mg
<u>ROUTE OF ADMINISTRATION:</u>	Oral
<u>DISPENSED:</u>	<u> X </u> Rx <u> </u> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

β -D-Xylan,(1-4),2,3-bis(hydrogen sulfate), sodium salt

Empirical Formula: $[C_5H_8O_4(SO_3Na)_2]_n$ where $n \approx 11$

Molecular Weight: 3676 average



The basic unit of pentosan polysulfate sodium (PPS) is comprised of one uronic acid substituent for every ten xylose units, and most of the hydroxyls are substituted with sodium sulfate groups. The total formula of such a unit is thought (ideal model) to be $C_{57}H_{108}O_{107}S_{21}Na_{22}$, the relative molecular weight of such a unit is 3676; hence an average monomer has a molecular weight of 333.74 (3676/11). Therefore, the theoretical number of sugar units (as xylose) in an average PPS chain is estimated to be in the neighborhood of 11-12 which is in agreement with the structural formula of a xylose disaccharide with repeating units of 3 to 6. The data submitted by _____ in the DMF have demonstrated consistency in the production of PPS from 1979 to date. There are no differences in the average molecular weight based on gel chromatography.

Supporting Documents:

DMF
 DMF
 DMF (Baker Norton Pharmaceuticals)---- Manufacture of drug product
 DMF

Related Documents:

IND

Consults:

Establishment Evaluation Request sent 1/11/93
 Environmental Assessment needed for Miami site
 Pharmacology - Approvable with labeling changes 12/20/91

Remarks:

Elmiron was granted an Orphan Drug designation for the treatment of interstitial cystitis 8/7/85. The clinical development of Elmiron was sponsored formerly by _____ under IND _____ Sponsorship was transferred to _____

_____ Baker Norton Pharmaceuticals, Inc. October 1992. Elmiron has been provided to over 1,274 interstitial cystitis patients on request by their physicians since 1986.

NDA 20-193

3

CONCLUSIONS & RECOMMENDATIONS:

This application is not approvable as yet. We are still awaiting a response to the deficiencies faxed 8/31/93.

Patricia Stewart
Review Chemist

cc:
Orig. NDA 20-193
HFD-160/Division File
HFD-102/Kumkumian
HFD-160/Chem/Stewart
HFD-160/Dir/Love
HFD-160/Pharm/See
HFD-160/CSD/Rhee

G.B. Shinn
10-21-93

Division of Medical Imaging, Surgical and Dental Drug Products
Review of Chemistry, Manufacturing, and Controls

AUG - 3 1993

NDA #: 20-193

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 5/28/93

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-19-91	06-19-91	07-02-91
AMENDMENT	12-10-92	12-11-92	12-14-92

NAME & ADDRESS OF APPLICANT:

Baker Norton Pharmaceutical
8800 N.W. 36th Street
Miami, Florida 33178-2404
Contact: Edward Gubish, Ph.D.
(303) 590-2617

DRUG PRODUCT NAME

<u>Proprietary:</u>	Elmiron
<u>Nonproprietary/Established/USAN:</u>	Pentosan Polysulfate Sodium
<u>Code Name/#:</u>	SP-54, PZ-68, PPS, USAN Z-41
<u>Chem.Type/Ther.Class:</u>	1 C

PHARMACOLOGICAL CATEGORY/INDICATION: Non-steroidal anti-inflammatory agent
for the treatment of interstitial cystitis

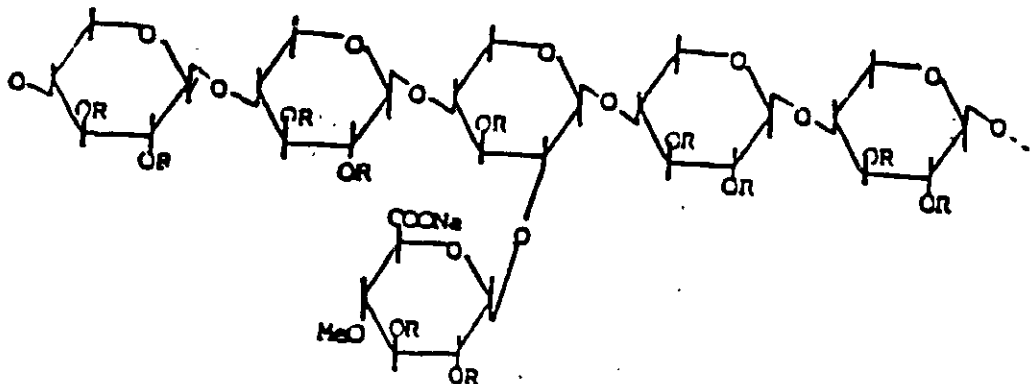
<u>DOSAGE FORM:</u>	Capsule
<u>STRENGTHS:</u>	100 mg
<u>ROUTE OF ADMINISTRATION:</u>	Oral
<u>DISPENSED:</u>	☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

β -D-Xylan,(1-4),2,3-bis(hydrogen sulfate), sodium salt

Empirical Formula: $[C_5H_6O_4(SO_3Na)_2]_n$ where $n \approx 11$

Molecular Weight: 3676 average



The basic unit of pentosan polysulfate sodium (PPS) is comprised of one uronic acid substituent for every ten xylose units, and most of the hydroxyls are substituted with sodium sulfate groups. The total formula of such a unit is thought (ideal model) to be $C_{67}H_{100}O_{107}S_{21}Na_{22}$, the relative molecular weight of such a unit is 3676; hence an average monomer has a molecular weight of 333.74 (3676/11). Therefore, the theoretical number of sugar units (as xylose) in an average PPS chain is estimated to be in the neighborhood of 11-12 which is in agreement with the structural formula of a xylose disaccharide with repeating units of 3 to 6. The data submitted by _____ in the DMF have demonstrated consistency in the production of PPS from 1979 to date. There are no differences in the average molecular weight based on gel chromatography.

Supporting Documents:

DMF
DMF
DMF (Baker Norton Pharmaceuticals)---- Manufacture of drug product
DMF

Related Documents:

IND

Consults:

Establishment Evaluation Request sent 1/11/93
Environmental Assessment needed for Miami site
Pharmacology - Approvable with labeling changes 12/20/91

Remarks:

Elmiron was granted an Orphan Drug designation for the treatment of interstitial cystitis 8/7/85. The clinical development of Elmiron was sponsored formerly by _____ under IND _____ Sponsorship was transferred to _____ Baker Norton Pharmaceuticals, Inc. October 1992. Elmiron has been provided to over 1,274 interstitial cystitis patients on request by their physicians since 1986.

CONCLUSIONS & RECOMMENDATIONS:

This application is not approvable from the standpoint of manufacturing and controls.

Patricia Stewart
Review Chemist

W. B. Shemin
2-3-93

cc:
Orig. NDA 20-193
HFD-160/Division File
HFD-102/Kumkumian
HFD-160/Chem/Stewart
HFD-160/Dir/Love
HFD-160/Pharm/See
HFD-160/CSO/Rhee

21.2

Division of Medical Imaging, Surgical and Dental Drug Products
Review of Chemistry, Manufacturing, and Controls

DEC 18 1991

NDA #: 20-193
CHEMISTRY REVIEW #: 1

DATE REVIEWED: 11-15-91

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	06-19-91	06-19-91	07-02-91

NAME & ADDRESS OF APPLICANT:

Baker Cummins Pharmaceutical
9800 N.W. 36th Street
Miami, Florida 33178-2404
(303) 590-2200

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/Established/USAN:
Code Name/#:
Chem.Type/Ther.Class:

Elmiron
Pentosan Polysulfate Sodium
SP-54, PZ-68, PPS, USAN Z-41

1 C

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

Non-steroidal anti-inflammatory agent
for the treatment of interstitial
cystitis

DOSAGE FORM:

Capsule

STRENGTHS:

100 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

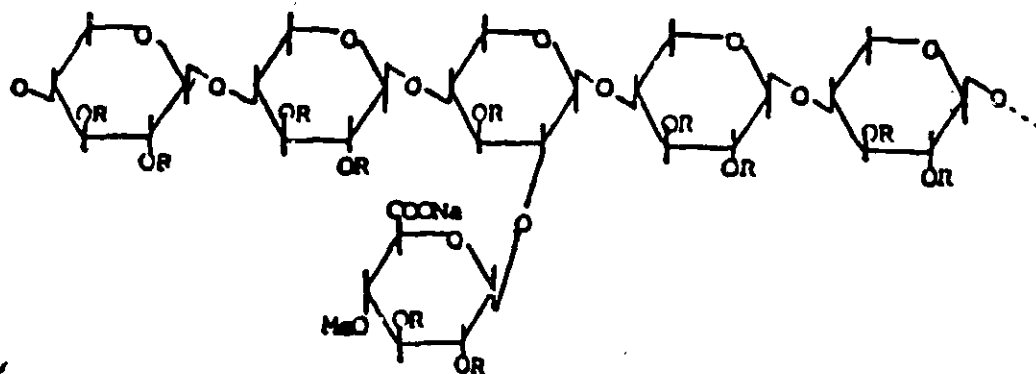
Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

beta-D-Xylan,(1-4),2,3-bis(hydrogen sulfate), sodium salt
(1-4)-beta-D-Xylan 2,3-bis(hydrogen sulfate), sodium salt

Empirical Formula: $[C_5H_8O_4(SO_3Na)_2]_n$ where $n \approx 17$

Molecular Weight: 5700 average



Supporting Documents:

DMF
DMF
DMF
DMF
DMF

DMF

Comments:

was transferred to DMF

was acquired by
. The information in DMF

Related Documents:

IND

Consults:

Establishment Evaluation Request sent 8/29/91 and 10/25/91
Environmental Assessment-deficient per P.Vincent 10/24/91
Pharmacology sent 11/14/91

Remarks:

Elmiron was granted an Orphan Drug designation for the treatment of interstitial cystitis 8/7/85. The clinical development of Elmiron was sponsored formerly by _____ under IND _____ Sponsorship was transferred to _____

Elmiron has been provided to over 1,274 interstitial cystitis patients on request by their physicians since 1986.

CONCLUSIONS & RECOMMENDATIONS:

This application is not approvable from the standpoint of manufacturing and controls.

Patricia Stewart
Patricia Stewart
Review Chemist

EB Stewart
12-18-91
WMC 12/30/91

cc:
Orig. NDA 20-193
HFD-160/Division File
HFD-102/C.Kumkumian
HFD-160/Chem/P.Stewart
HFD-160/MO/Kenzaly
HFD-160/Pharm/Dewitt
HFD-160/CSO/Phoo

FEA And
Fonsi

FINDING OF NO SIGNIFICANT IMPACT

AND

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-193

Elmiron

(pentosan polysulfate sodium)

Capsules 100 mg

**DIVISION OF MEDICAL IMAGING, SURGICAL AND
DENTAL DRUG PRODUCT (HFD-160)**

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

**FINDING OF NO SIGNIFICANT IMPACT
NDA 20-193**

**Elmiron
(pentosan polysulfate sodium)
Capsules 100 mg**

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food And Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

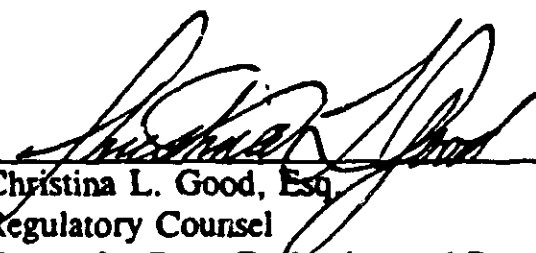
The FDA, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Elmiron (pentosan polysulfate sodium) Capsules, 100 mg, an orphan drug, Baker Norton Pharmaceuticals, Inc. has prepared an abbreviated environmental assessment (EA) for a drug in the prevention, treatment, or diagnosis of a rare disease or similarly infrequent use (21 CFR 25.31a(b)(3) (attached)). The EA evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Elmiron Capsules is a drug which is administered as a capsule for the symptomatic treatment of patients suffering from interstitial cystitis (IC). The finished drug product will be primarily used in a variety of settings such as patients' homes, hospitals and nursing homes. Because of the low volume and controls on production and the low volume of use of this orphan drug, the expected concentrations emitted to the environment from this drug are not expected to be toxic to organisms. Precautions at the manufacture facilities also are expected to minimize occupational exposures and environmental release. Accidental spill control procedures are available. Disposal will be in accordance with appropriate waste procedures. Adverse effects are not anticipated upon endangered species or historic sites listed in or eligible for listing in the National Register of Historic Places.

CDER has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects.

11/15/95
DATE


Christina L. Good, Esq.
Regulatory Counsel
Center for Drug Evaluation and Research

11/16/95
DATE


Concurrence

Attachment:

FOI Copy of Environmental Assessment for Elmiron Capsules, 100 mg

OK

file:fonsi 20193e01.fcg

cc:
HFD-160
HFD-357/file 20-193
docket copy
FOI copy

FOI

Baker Norton Pharmaceutical, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404

Elmiron®
NDA#20-193
Environmental Assessment of Elmiron®

August 30, 1995

000002

ENVIRONMENTAL ASSESSMENT - ELMIRON®

1.0 DATE

May 19, 1993

Revised April 14, 1995

Revised August 30, 1995

2.0 NAME OF APPLICANT/PETITIONER

Baker Norton Pharmaceuticals, Inc.

3.0 ADDRESS

8800 Northwest 36th Street, Miami, Florida 33178-2404

4.0 DESCRIPTION OF PROPOSED ACTION

4.1 Requested Approval

The proposed action involves the drug for human use, Elmiron® (active ingredient: pentosan polysulfate sodium). Elmiron® is used for the symptomatic treatment of patients suffering from interstitial cystitis (IC), for which Baker Norton submitted a New Drug Application (NDA 20-193) for the manufacturing, processing, packaging, labeling and distribution of Elmiron® 100 mg capsules.

As Baker Norton Pharmaceuticals, Inc. is requesting approval of Elmiron® for use in treatment of IC, an environmental assessment (EA) is required to comply with the FDA's implementation of the National Environmental Policy Act. Elmiron® has orphan drug status under the Orphan Drug Act (Appendix B-1), and as such, is considered a drug for human use intended for the treatment of this rare disease. Consequently, the following documentation is provided in the EA format described in 21 CFR 25.31a (b) (3) (i) and (ii) applicable to human use drugs and biological products intended for the prevention, treatment, or diagnosis of a rare disease.

000003

In support of this EA, Baker Norton Pharmaceuticals Inc., has referenced Drug Master File . The manufacturers of the active ingredient (pentosan polysulfate sodium) in Elmiron® have given Baker Norton Pharmaceuticals, Inc. the authority to reference the Drug Master File (Appendix B-2).

4.2 Need for the Action

Elmiron® is used in the symptomatic treatment of interstitial cystitis (IC). Interstitial cystitis is microscopically characterized by a nonspecific chronic inflammatory infiltrate, edema and vasodilatation of the submucosa and detrusor layers of the urinary bladder wall. In the healthy bladder, the bladder mucosa is lined by a layer of sulfonated glycosaminoglycans (GAGs). This layer serves as an important barrier against bacteria and as a protective layer against toxic substances (e.g. chemical, carcinogens, allergens) in the urine. However, in IC patients, a functionally deficient GAG layer results in urine penetrating into the deeper layers of the bladder (submucosa, detrusor) and inducing an inflammatory response with deposition of mast cells. This causes symptoms of bladder irritation such as increased urinary frequency, nocturia and pain. Elmiron® is an orally bioavailable, highly sulfated polysaccharide, and acts as a synthetic polyionic agent augmenting the deficient GAG layer found in IC patients.

The prevalence of IC in the United States is estimated to be about per 100,000 women and the ratio of affected women to men is about 10:1. The overall patient population in the United States is estimated to be in 1994. Due to the rare nature of this condition in the general population of the United States, Elmiron® has obtained orphan drug status as defined in 25 CFR part 316 (Appendix B-1).

000004

4.3 Production and Processing Locations and Environments

Elmiron® will be produced for the proposed action in a facility owned and operated by Baker Norton Pharmaceuticals, Inc., 8800 Northwest 36th Street, Miami, Florida 33178-2404. The production of Elmiron® 100 mg capsules is described in Appendix B-3.

The active ingredient, pentosan polysulfate sodium is manufactured in its entirety by

This facility is located in a residential neighborhood. has provided Baker Norton with documentation of the German original and a certified translation of the License for pentosan polysulfate sodium-production site granted by the Federal Land Capitol of Munich (Appendix A-1).

The Elmiron® capsules are bottled and packaged on-site at the Baker Norton Pharmaceuticals, Inc. facility at 8800 NW 36 St., Miami, Florida. No outside facilities are utilized for packaging, repackaging, processing, reprocessing, labeling, or warehousing.

The Baker Norton Pharmaceuticals, Inc. facility at 8800 NW 36 St., Miami, Florida is located in a light-industrial area with no adjacent residential properties. The Baker Norton property is adjacent to Florida Power and Light (South), vacant land (Southwest), the Dressel Dairy Canal (Southeast), and the Doral Country Club (North) (Appendix B-4). The location in the facility where Elmiron® is manufactured is the Production Department which is equipped for production of pharmaceutical products (Appendix B-5).

The facility at 8800 NW 36 St., Miami, Florida 33178, where the Elmiron® capsules are manufactured, holds an industrial waste pollution control permit (permit number is IW-00334-93) with DERM (Dade County Environmental Resource Management Agency) (Appendix A-2). This pollution permit covers the amount of wastewater sent into the sewer, and the types of wastes generated. Baker Norton Pharmaceuticals, Inc. provides DERM a report on the preceding items on a monthly basis.

Wastes or emissions related to the production of Elmiron® at the Baker Norton facility would be discharged directly to the sanitary sewers. To date Elmiron® wastes have not been disposed of by outside contractors.

In the event of the need for disposal of rejected or out-of-specs Elmiron®, two licensed waste disposal contractors,

have been identified

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for use. These outside waste disposal contractors are presently used by Baker Norton to dispose of other waste materials generated on-site but unrelated to the production of Elmiron®.

4.4 Use and Disposal Locations and Environments

Elmiron® 100 mg capsules, as a prescription drug, will be dispensed by registered pharmacists throughout the U.S. for use by IC patients in a variety of settings such as patients' homes, hospitals and nursing homes. The vast majority of capsules will be consumed by patients, primarily resulting in the disposal of the empty containers only in municipal solid waste facilities throughout the U.S. Patient use of Elmiron® would result in the excretion of metabolized and unmetabolized drug to municipal sanitary sewage treatment facilities in the U.S.

5.0 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

5.1 Physical and Chemical Data

Name: Pentosan polysulfate sodium (PPS); sodium pentosan polysulfate; sodium xylan polysulfate; SP 54; Thrombocid.

Chemical Abstracts Registry No.: 116001-96-8

Molecular Formula/Weight: $[C_5H_6Na_2O_{10}S_2]_n$ (n=6 to 12) as listed in the USP Dictionary for USAN and International Drug Names (Appendix A-3). The molecular weight range of 4000-6000 Daltons was quoted by _____ to the USP Dictionary for USAN and International Drug Names (Appendix A-3). For more detailed information see Appendix B-6.

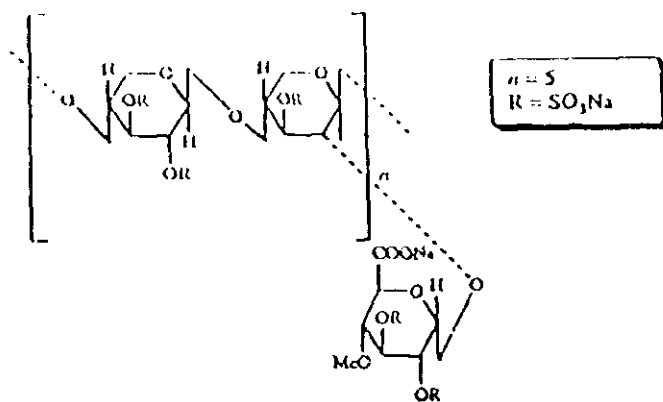
Physical Description: White, odorless and a slightly hygroscopic powder; very soluble in water (about 7g in 10 mL; n-octanol/water coefficient of approximately 0); aqueous solutions of PPS are slightly acidic (a 10% solution has a pH of about 6.0).

Impurities: The following impurities are controlled by testing performed by _____ the drug substance manufacturer, and are required to be tested by internal specifications (Appendixes B-7, 8).

- Sodium sulfate
- Methanol
- Free pyridine
- Heavy Metals

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Structural Formula.



Drug Product Composition: The drug product composition is provided in Appendix B-9.

Starting Materials for PPS: The starting materials for the manufacture of PPS are given in Appendix B-10 along with their CAS numbers.

Note: These materials are used to manufacture the active ingredient PPS at _____ and _____ are not used for the US manufacture of the final drug product Elmiron®. Physical and chemical information on these substances is provided in Appendix B-11.

Material Safety Data Sheets: The MSDSs for the active ingredient and finished product are attached in Appendixes A-4, 5. The MSDSs for all other raw materials used in the production of PPS and Elmiron® are attached in Appendixes B-12, 13.

Acute Toxicity: Pentosan polysulfate sodium meets the definition of being "practically non-toxic" based on oral LD₅₀ of greater than 35 g/kg in rodents (Appendix B-14). There was no meaningful species or sex sensitivity by any of the routes of administration tested. The principle signs during life were apathy and dyspnea; postmortem signs in animals which died from very high doses were hemorrhaging into the pleural and peritoneal spaces.

Information pertaining to the active ingredient is contained in the Drug Master File _____. Authorization from _____ to reference this information has been given to Baker Norton in support of the EA of Elmiron® (Appendix B-2).

5.2 Production Process

A description of the Elmiron® production process, including a flow diagram, is given in Appendix B-3.

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5.3 Polymer Characteristics

By using gel chromatography, molecules can be separated based on their relative size, permitting a rough estimate of the most common polymer size. The results of GPC analyses performed on the release tests of pentosan, the unsulfated intermediate in the PPS production are confidential and are presented in Appendix B-15. The intermediate, pentosan, was analyzed instead of pentosan polysulfate sodium, as the latter substance does not exhibit separate peaks within the Gaussian curve. This methodology does not permit an exact quantitative determination of the relative percentages of polymer sizes; however, the size determined by GPC corresponds well with the results of molecular weight determination experiments utilizing a light scattering method (Appendix B-6).

5.4 Impurity Monitoring

Methodologies utilized by _____ to analyze impurities, [sodium sulfate, methanol, free pyridine and heavy metals (Appendix B-7, 17)] in the active ingredient, pentosan polysulfate sodium, are provided in Appendix B-8.

5.5 Metabolic Products

The metabolism of pentosan polysulfate sodium (PPS) in humans has been evaluated in several studies (Appendix B-18). By using ^3H and ^{125}I -radiolabeled PPS, the biotransformation profile of PPS after single i.v. and oral administration has been assessed. It appears that PPS metabolism (i.e. desulfation and depolymerization) is time- and dose-dependent based on experimental results. Desulfation is thought to occur within the liver and spleen whereas depolymerization is believed to occur in the kidney.

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Based on single oral doses of 2, 5, and 10 mg/kg of tritium-labeled PPS to three human subjects, it was determined that the majority of PPS is excreted through the feces (66.9% to 57.4% radioactivity) rather than through renal excretion (3.4-3.5% radioactivity) (Appendix A-6). These data suggest that biliary excretion is the primary route of elimination for the radiolabeled PPS. The radiolabeled PPS was also extensively metabolized (depolymerized, desulphated fragments), with negligible amounts of the parent drug found in the urine of the human subjects.

The daily therapeutic dose of Elmiron® is 300 mg (3 capsules) which suggests much of the original dose will be excreted as metabolized PPS in the feces rather than in the urine. In patients treated for interstitial cystitis with PPS, urinary concentration of PPS ranged from 0.8-16 mg/mL (Appendix A-7).

5.6 Raw Materials

The copper beech tree (*Fagus sylvatica*) is utilized in the production of the active ingredient, pentosan polysulfate sodium, by This
hardwood species is not considered an endangered species. The harvest and extraction procedures are conducted in Germany and are in accordance with all local forestry regulations in Germany. German policies regarding harvestation and reforestation were specified in a letter to the FDA, Center for Drug Evaluation and Research dated April 16, 1991 (Appendix B-19).

6.0 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Production of Drug Substance

6.1.1 Site of Production

6.1.2 Environmental Permits

The manufacturer of the active ingredient, pentosan polysulfate sodium, is

This site is located in a predominately residential neighborhood. This firm is in compliance with local, state and federal environmental laws in Germany. Such a production site must be approved and controlled by the Department of the Environment of the city of Munich (Umweltschutzreferat der Landeshauptstadt München). This approval is granted only if the facility operates in accordance with environmental regulations. In 1985, such an approval was granted by the above mentioned authority to

This document is 27 pages in length. A certified translation of the first two pages (stating that the production site is approved) and the last page (with the signature) is included (Appendix A-1). The other pages contain confidential information belonging to

This document, in both German and English, has been added by
to their DMF.

6.1.3 Manufacturing Emissions

The substances expected to be emitted at the are detailed in Appendix B-20). Brief descriptions of the waste solutions and emissions are given below:

Waste Solutions: Mother liquids containing the reaction products and some starting materials and solvents are collected and destroyed by a special waste processing company. All other solutions containing only starting materials are eliminated by sewage. This is in accordance with the notice of the local authorities (Umweltschutzreferat der Landeshauptstadt München).

Gaseous Emissions: All gaseous emissions comply with the German Bundesimmissionschutzgesetz as stated in the notice of the local authorities (Umweltschutzreferat der Landeshauptstadt München). The gaseous emissions are measured at regular intervals using a FID (Flame Ionization Detector).

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Others: During the processing of the wood grains and the subsequent esterification, no hazardous emissions - neither gaseous, liquid or solid - are generated.

Estimated quantities of substances expected to enter the environment per day as a result of use and/or disposal of product affected by the action are described in Appendix B-21.

6.2 Production of Drug Product

6.2.1 Site of Production

Baker Norton Pharmaceuticals, Inc., 8800 N.W. 36th Street, Miami, Florida 33178

6.2.2 Environmental Permits

Baker Norton Pharmaceuticals facility at 8800 NW 36 St., Miami, Florida 33178, holds an industrial waste pollution control permit with DERM (Dade County Environmental Resource Management Agency) (Appendix A-2). The permit number is IW-00334-93. This pollution permit covers the amount of wastewater sent into the sewer and the type of wastes generated. Baker Norton Pharmaceuticals sends DERM a monthly report on the preceding items. The Baker Norton Pharmaceuticals facility is in compliance with all pertinent regulations governing environmental emissions (Appendix A-8).

6.2.3 Manufacturing Emissions

The final product, Elmiron® Capsules, are produced by a dry blend encapsulation process, then packaged into final containers. The quantities of substances emitted into the environment throughout this process are minimal.

Waste Solutions:

One batch per week is manufactured of Elmiron®. The Elmiron® is weighed, blended, and encapsulated. It is calculated that < (or approximately less than /week of Elmiron®) becomes waste as measured by the amount of powder collected when vacuum cleaning the encapsulation machine after the operation is over. The vacuum cleaner is washed down in the Wash Room (Appendix B-5) where the wastewater goes into the sanitary sewers.

Plant Emissions Control:

Based on a weekly production rate of kg of Elmiron®, only a very small amount of the calculated Elmiron® waste is expected to be captured by the Torit air filter system in the room where the Elmiron® is manufactured. The Torit unit is a portable unit that recirculates the air inside the room with no emission to the outside. The amount trapped in the filter is of such small quantities that the filter has not required changing in more than one year. Cleaning of the filter unit would involve flushing the filter with water, thus any dusts generated during the manufacturing process would be discharged to sanitary sewers.

6.3 Disposal Practices of Drug Product Manufacturer

Baker Norton Pharmaceuticals, Inc., uses two outside disposal contractors .

However, neither service has been used to date to dispose of out-of-specification and/or recalled Elmiron® products as no such disposal was required. If disposal for out-of-specification and/or recalled drug products were to become necessary, one of the two services would be contacted for disposal. operates a local incinerator approved for biomedical waste. also will take non-regulated waste like Elmiron® for incineration. Before incineration, the waste load must be approved by DERM (Dade County Environmental Resource Management agency). is the largest hazardous and non-regulated waste disposal company in the country, and is well equipped to meet all local, state, and federal regulations regarding waste disposal. disposes of waste with fuel blending techniques. Environmental permits for both companies are included in Appendixes A-9, 10.

6.4 Effect of Approval upon Compliance with Current Emission Requirements at Production Site

FDA approval of the EA of Elmiron® is not expected to affect the current emission requirements at the Baker Norton Pharmaceuticals facility at 8800 NW 36 St., Miami, Florida 33178 as to meet the anticipated marketing forecasts (see 6.5), will not result in a significant increase in weekly production over and above of Elmiron®. Consequently, the amount of Elmiron® waste produced will not be significantly greater than per a week.

6.5 Estimates of Maximum Yearly Market Volume of Drug Product

The following table includes a preliminary proposed forecast on production of Elmiron® 100 mg Capsules (bottles of 100) for 5 years.

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Bottles of 100					

These preliminary forecasts for Elmiron® were derived by using the estimate of patients reported from IMS with a trial usage of of that patient population. Given that Elmiron® appears to have a response rate, sales forecasts were estimated at bottles per responder and bottles for the balance of non-responders.

The patient population growth reported from IMS is an average of over the past three years. Using this information, the five year forecast was estimated based on a growth of over the next four years with the trial usage decreasing from year one to year two and years three through five.

On the basis of this preliminary marketing plan, the maximum yearly market volume is estimated to be bottles of 100 Elmiron® 100 mg capsules. This equates to a maximum production of approximately of Elmiron® per year.

7.0 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

In accordance with 21 CFR 25.31 (a) (3) (ii) regarding the approval of an NDA for a human drug when the drug is intended for the prevention, treatment or diagnosis of a rare disease, documentation for format item 7 is ordinarily not required. As Elmiron® (active ingredient: pentosan polysulfate sodium) has Orphan Drug status for the treatment of interstitial cystitis, format item 7 is not applicable to this environmental assessment.

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

In accordance with 21 CFR 25.31 (a) (3) (ii) regarding the approval of an NDA for a human drug when the drug is intended for the prevention, treatment or diagnosis of a rare disease, documentation for format item 8 is ordinarily not required. As Elmiron® (active ingredient: pentosan polysulfate sodium) has Orphan Drug status for the treatment of interstitial cystitis, format item 8 is not applicable to this environmental assessment.

9.0 USES OF RESOURCES AND ENERGY

In accordance with 21 CFR 25.31 (a) (3) (ii) regarding the approval of an NDA for a human drug when the drug is intended for the prevention, treatment or diagnosis of a rare disease, documentation for format item 9 is ordinarily not required. As Elmiron® (active ingredient: pentosan polysulfate sodium) has Orphan Drug status for the treatment of interstitial cystitis, format item 9 is not applicable to this environmental assessment.

10.0 MITIGATION MEASURES

In accordance with 21 CFR 25.31 (a) (3) (ii) regarding the approval of an NDA for a human drug when the drug is intended for the prevention, treatment or diagnosis of a rare disease, documentation for format item 10 is ordinarily not required. As Elmiron® (active ingredient: pentosan polysulfate sodium) has Orphan Drug status for the treatment of interstitial cystitis, format item 10 is not applicable to this environmental assessment.

11.0 ALTERNATIVES TO THE PROPOSED ACTION

In accordance with 21 CFR 25.31 (a) (3) (ii) regarding the approval of an NDA for a human drug when the drug is intended for the prevention, treatment or diagnosis of a rare disease, documentation for format item 11 is ordinarily not required. As Elmiron® (active ingredient: pentosan polysulfate sodium) has Orphan Drug status for the treatment of interstitial cystitis, format item 11 is not applicable to this environmental assessment.

12.0

ENVIRONMENTAL RISK ASSESSMENT

Information presented in the preceding sections identified surface waters as the environmental compartment that would receive Elmiron® wastes via discharges to sanitary sewers related to the manufacture of the drug product and excretion through patient use. Upon release to the aquatic environment pentosan polysulfate sodium, the active drug ingredient, would be expected to be distributed within the water column due to its high water solubility (7 g in 10 mL). Since this chemical is primarily a polymer of xylose sugars it would likely be subject to some biodegradation in the environment.

No information was identified on the potential toxicity of pentosan polysulfate sodium to aquatic species or terrestrial wildlife; however, in the absence of such data an assessment of aquatic toxicity can be elucidated on the basis of structure activity relationships noted for this class of organic chemicals (Appendix A-11). Pentosan polysulfate sodium is a highly charged macromolecule which typically would not be expected to be absorbed through respiratory membranes. Charged polymers with MWs > 1000 are unable to cross gill membranes of aquatic species and therefore are not considered to be systemic toxicants but act only through a surface active toxic mechanism (Appendix A-12, 13). Polyanionic polymers readily bind positively charged ions in aqueous solutions and thereby may adversely affect the availability of nutrient elements in aquatic environments (Appendix A-11). Water soluble polymer pentosan polysulfate with an average MW ranging from approximately 3,000 to 6,000 would not be expected to be absorbed through biological membranes. Any adverse effects in aquatic species related to this chemical would be expected to be due to the direct action of the chemical on the outer membranes of aquatic organisms (i.e., gills) or through the overchelation of nutrient elements. In the absence of any aquatic toxicity data for polyanionic polymers, the average polyanionic monomer may provide the best available reference effective concentration with an algal EC₅₀ of about 3 mg/L (Appendix A-11).

A definitive assessment of the potential impacts of the active ingredient, pentosan polysulfate sodium on aquatic life was not possible due to a lack of available information on the aquatic toxicity of this chemical. However, an estimate of the maximum annual production of Elmiron® of _____ suggests that only small releases of pentosan polysulfate sodium distributed across the U.S. would be expected to occur. The largest point source of Elmiron® to the aquatic environment would be the Baker Norton facility which has been estimated to discharge _____ batch to the sanitary sewers of which _____ would be pentosan polysulfate sodium. This _____ /batch discharge would occur during a one day period, after each batch is completed. Miami has a daily total waste water flow rate of 120 million gallons. Thus, the maximum expected emitted concentration of pentosan polysulfate to the aquatic environment

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related to these activities would be . Actual concentrations of pentosan polysulfate sodium in the aquatic environment would be further diluted through mixing of treated waste waters with receiving waters.

The maximum expected emitted concentration concentrations of pentosan polysulfate sodium related to patient use, assuming that 100% of the drug would be excreted unmetabolized, would be . Actual environmental concentrations of pentosan polysulfate sodium related to patient use would be less than since, i) the IC patients are distributed across the U.S. and the excreted drug would not enter the same water body but would occur throughout the U.S., and ii) concentrations in treated waste waters would be further diluted through mixing with receiving waters.

These maximum expected emitted concentration of pentosan polysulfate sodium related to manufacturing and patient use are about orders of magnitude respectively less than the reference concentration of 3 mg/L for adverse effects of polyanionic monomers in green algae. Therefore, based on this cursory assessment of the potential impact of emissions related to the manufacture and patient use of Elmiron® in the U.S., no adverse effects on aquatic species would be expected to occur at the maximum predicted environmental concentrations. The calculations and the assumptions used to arrive at these figures are presented below.

Furthermore, these predicted environmental concentrations would correspond to a maximum estimated exposure of body weight/d for the average adult male, assuming a daily water consumption of 2 L, a body weight of 70 kg, and no degradation of the active drug pentosan polysulfate sodium through sewage treatment, natural surface water and drinking water treatment processes. This estimated maximum exposure would be about less than the therapeutic dose of body weight/d, or mg pentosan polysulfate sodium per 70 kg individual per day. Therefore, no adverse effects on human health or environmental health would be expected to occur at these predicted maximum environmental concentrations of pentosan polysulfate through the manufacture and use of Elmiron® for the treatment of interstitial cystitis.

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Estimated Maximum Annual Production of Elmiron®

Based on the preliminary 5 year marketing plan (see section 6.5)

$$\begin{aligned} & (\quad \text{bottles/y}) \times (100 \text{ capsules/bottle}) \times (100 \text{ mg/capsule}) \div 1000 \text{ mg/g} \\ & = \quad \text{g/y} \\ & = \quad \text{kg/y} \end{aligned}$$

Maximum Expected Emitted Concentration of Pentosan Polysulfate to Surface Waters from the Baker Norton Facility

The maximum concentration of pentosan polysulfate that would be expected to occur in surface waters was conservatively estimated to be $\mu\text{g/L}$, according to the following calculations:

$$\begin{aligned} \text{kg/day} \div (454,240 \text{ m}^3/\text{d}) &= \quad \text{kg/m}^3 = \\ \text{g/L} &= \quad \text{mg/L} = \quad \mu\text{g/L} \end{aligned}$$

assuming,

- i) each batch will produce approximately $\quad$ kg of Elmiron® waste, which will be disposed of during one day after the completion of a batch.
- ii) $\quad$ % of the Elmiron® waste discharge to sanitary sewers related to drug manufacture would be pentosan polysulfate sodium;
- iii) 0% degradation of pentosan polysulfate in the sewage treatment; and
- iv) a total waste water flow rate of 120 million gallons per day (MGL) (454,240 m^3/day) for Miami.

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Maximum Expected Emitted Concentration of Pentosan Polysulfate Sodium in Surface Waters Related to Individual Patient Use

The maximum concentration of pentosan polysulfate sodium in surface waters through patient use was estimated to be $\mu\text{g/L}$. This was based on the following calculation and assumptions:

$$\begin{aligned} \text{lbs/y} \times 8.9 \times 10^{-9} \text{ (equation constant)} &= \text{ppm} \\ &= \text{mg/L} \\ &= \text{ug/L} \end{aligned}$$

This equation is more fully described in the Appendix A-14, Pharmaceutical Manufacturers Association: Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA, 1991 assuming,

- i) an estimated maximum annual drug production of kg/y (see 6.5);
- ii) 100% of the drug would be excreted unmetabolized;
- iii) an average daily waste water generated per individual of 150 gallons; and
- iv) 246 million persons.

The above calculations conservatively assumes that 100% of the PPS ingested is excreted as unmetabolized PPS. However, clinical studies indicate that PPS is metabolized extensively in the human body to short chain, desulphated fragments (see section 5.4).

13.0 LIST OF PREPARERS

Dr. Helmut Benend	Director of Quality Control for bene-Arzneimittel GmbH for 5 years and a pharmacist by training since 1982.
Alfredo Delregato	Safety and Environmental Manager with a BS degree in Biology and Environmental Sciences and 10 years of industrial experience.
Dr. Edgar Mitchell	Vice President of Regulatory Affairs with a Ph. D. in Pharmacology and 20 years of industrial experience in Clinical Pharmacology, Pharmaceutical Research and Regulatory Affairs.

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14.0

CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of Baker Norton Pharmaceuticals' knowledge.

NAME: Edgar W Mitchell TITLE: V.P. Regulatory Affairs
Edgar W Mitchell 10/26/95
Signature Date

15.0

REFERENCES

- Auer, C.M., Nabholz, J.V., and Baetcke, K.P. 1990. Mode of action and the assessment of chemical hazards in the presence of limited data: Use of structure-activity relationships (SAR) under TSCA, Section 5. *Environ Health Perspect* 87:183-197.
- Callahan, H.J., Shupp-Byrne, D., Pizzo, M., Parsons, C.L., Mulholland, S.G. 1991. The production of antibodies to pentosanpolysulfate (ELMIRON, SP-54). *Journal of Immunological Methods*, 136:53-59.
- Nabholz, J.V., Clements, R.G., Zeeman, M.G., Osborn, K.C., and Wedge, R. 1993a. Validation of Structure Activity Relationships used by the U.S. EPA's Office of Pollution Prevention and Toxics for the Environmental Hazard Assessment of Industrial Chemicals. *In: Environmental Toxicology and Risk Assessment: 2nd Volume, ASTM STP 1173.* Gorsuch, J.W., Dwyer, F.J., Ingersoll, C.G., and LaPoint, T.W., (Eds.). American Society for Testing and Materials, Philadelphia.
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- Hazleton Laboratories, 1984. Metabolism and Pharmacokinetics of Sodium Pentosan Polysulphate.
- Pharmaceutical Manufacturers Association, 1991. Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. Appendix III: Calculation of Maximum Expected Emitted Concentration (MEEC).

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Appendix A

Non-Confidential Material - May Be Released

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1

BAKER NORTON PHARMACEUTICALS, INC.
Attn. of Steven M. Viti, Ph.D.
8800 NW 36th Street
Miami, Florida 33178

U. S. A.

im Zeichen

im Nachricht vom
March 13, 95

Datum
March 21, 1995

Dear Dr. Viti,

Attached please find the first two and the last page of the German version as well as a certified translation of the Licence for our PPS-production site granted by the Federal Land Capital of Munich, Environmental Protection Department on August 19, 1985. As we told you in our fax dated March 15, 1995, generally such a licence is only granted if a facility works in accordance with the environmental law (Federal Immission Control Act).

In case the FDA insists on the confidential pages 3 through 26, we will contact them immediately.

Best regards

Attachment

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- excerpt from the certified translation -

Rena Ilmberger
- duly registered, commissioned and sworn translator -

on behalf of

Made out this 20th day of March 1995

000025

Federal Land Capital of Munich
Environmental Protection Department

Office: Bayerstrasse 28a

Room no. 408

Clerk in charge: Herr Worthmann

dd 233/8558

File no. U-21 wo/A

date: 19-08-1985

Federal Land Capital of Munich, Environmental Protection Department, P.O. Box, 8000 Munich 1
Against acknowledgement of receipt

Subject:

Execution of the Federal Immission Control Act
(*Bundes-Immissionsschutzgesetz - BImSchG*)

Herterichstrasse 1

Chemical Production of Medical Drugs
Sodium pentosan polysulfate

As of the Application as per 21-12-1983, specified with the letter dated 09-11-1984, the Federal Land Capital of Munich, Environmental Protection Department, on behalf of the District Authority, gives the following

Notice:

I.

Licence:

Under the provisions of the following documents (II) and additional regulations (III) the establishment and operation of the plant described in the following will be subsequently

approved:

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Type of plant: chemical production of medical drugs, ester plant

Plant components: preparation flask (Jena glass 200 l volume)
agitator, reflux refrigerator, dropping funnel, mobile kettles,
filter funnels and presses, centrifuges, autoclaves,
circulation evaporators, drying cabinets and mills,
subterranean methanol tanks (30 m³), residue tank

Erection site:

Note: This approval does not replace authorized project, approvals as well as official decisions due to water-right regulations (§ 13 BImSchG = Federal Immission Control Act).

Any and all official decisions already passed with respect to the approved plant remain unaffected and shall furtheron be observed as provided, unless otherwise stated.

II.

Approved documentation and attachments:

a) Approved documentations:

Basement and plan including establishment of equipment

Application no per 21-12-1983 (hand-written)

09-11-1984

Description - Production of the preliminary product
- Esterification procedure
- Flux scheme including esterification and preparation

The plans and descriptions carrying the approval note by the environmental protection department shall be components of this approval.

The official marks and registrations entered in red colour shall be observed in detail.

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in order to file the opposition; this mailbox can be used to mail the opposition until 24.00 hours to observe the expiry term. This expiry is also guaranteed, if the opposition will in time be received by the Government of Upper Bavaria (Regierung von Oberbayern), Maximilianstrasse 39, 8000 Muechen 22.

In case in due course no technical decision had been made on such opposition without a sufficient reason, a written complaint or a complaint to be recorded by the official clerk of the court office could be filed to the Bavarian Administrative Court (Bayerisches Verwaltungsgericht) in 8000 Muenchen 2, Bayerstrasse 30. Such complaint cannot be filed until three months from the filing of such opposition, unless a shorter term is given due to the special circumstance of such case. The complaint must comprise the plaintiff, the defendant (Federal Land Capital of Munich) and the matter in dispute and should include a certain application. The facts and proofs serving for reasoning should be stated, the contested instruction be included in the original or copies be made thereof. Copies of the complaint and any and all documents should be included for the other parties involved.

This notice comprises 27 pages.

(signature)
Schmid-Drechsler
Senior administrative officer

This is to certify the foregoing translation to be a true and complete English version of the original document made out in the German language.

Duly registered, commissioned and sworn translator.

Munich made out this 20th day of March 1995

000028

2



INDUSTRIAL WASTE ANNUAL OPERATING PERMIT

ENVIRONMENTAL RESOURCES MANAGEMENT POLLUTION PREVENTION DIVISION SUITE 000 33 S W 2nd AVENUE MIAMI, FLORIDA 33130-1540 (305) 372-6017

PERMITTEE: Mr. Randy Glover IVAX CORP./BAKER MORTON PHARMACEUTICALS, INC. 8800 NW 36 ST MIAMI, FL 33178

PAGE 1 OF 1 PERMIT No.: IW-00334-95 (3) J 05 SOURCE NAME: IVAX CORP./BAKER MORTON PHARMACEUTICALS, INC. LOCATION: 8800 NW 36 ST MIAMI, FL 33178

DESCRIPTION OF FACILITY/EQUIPMENT:

This document, issued under the provisions of Chapter 24, Metropolitan Dade County Code (Dade County Pollution Control Ordinance), shall be valid from June 1, 1995 through May 31, 1996. The above named permittee is hereby authorized to operate the pollution control facility at the above location which consists of the following:

- Pharmaceutical products manufacturing facility including: A. Oil/water separator to receive floor washwater with a clean-out plug as a sampling point. B. Quality Control Laboratory with Hazardous Materials/Hazardous Waste Storage Area.

Subject to specific and general conditions listed below and in the following pages of this document (if any).

SPECIFIC CONDITIONS:

- 01 Hazardous waste, sludge and other industrial wastes and/or wastewater must be transported by DERM approved transporters. Analytical data must be submitted to DERM, for all waste and/or wastewater that is disposed of locally. Failure to gain approval from DERM, for disposal, will result in rejection of your waste at the disposal facility.
02 A monthly report of operations shall be submitted to this Department on or before the 15th of the following month including: copies of manifests and/or receipts of all hazardous waste, industrial waste and/or wastewater disposed of. Information shall include name of hauler, volume and final destination. Records shall be kept on the premises to be presented upon request.
03 A monthly report of operations shall be submitted to this Department on or before the 15th of the following month including: 1. Average daily wastewater flow (gals). 2. Analytical data from a certified laboratory for pH and Solvent Scan. 3. Amount of sludge disposed of, name of hauler and final destination. Please refer to the enclosed monitoring program.
04 All hazardous materials shall be kept in DOT approved containers. These containers shall be kept closed and stored in an approved storage area allowing aisle space to provide visual inspection of containers. Any spillage of materials must be addressed immediately and reported to this Department (372-6789) as required by Section 24-37(3) of the Metropolitan Dade County Code.
05 All above ground tanks and storage areas for hazardous materials and hazardous waste must have secondary containment. Design and construction must have departmental approval.
06 The Department of Environmental Resources Management requires the submittal of a formal Closure Plan to insure the proper removal/disposal of all hazardous/non-hazardous materials and/or wastes stored on site. The Closure Plan must be submitted for review and approval, a minimum of thirty (30) days prior to the cessation or relocation of operations. Please call 372-6600 for information on requirements.

Permit Number: 000010140

Metropolitan Dade County Department of Environmental Resources Management

Signature: Marya J. Flagler for Director

3

Attachment

United States Adopted Names Council
American Medical Association
P.O. Box 10970
Chicago, Illinois 60610

U.S.A.

Se Zuehen

Das Fachblatt von:

Datum

April 7, 1993

Re: Pentosan Polysulfate Sodium, USAN (Z - 41)

Dear Sirs,

Recent analytical and clinical results forced us to revise the description, the structural formula and the therapeutic claim of our substance pentosan polysulfate sodium (PPS).

Enclosed please find the revised definition.

A copy of this letter is being sent to the Senior Pharmaceutical Officer, Pharmaceuticals of the WHO in Geneva.

In case of any questions with regard to the above please do not hesitate to contact us.

Best regards

Enclosure

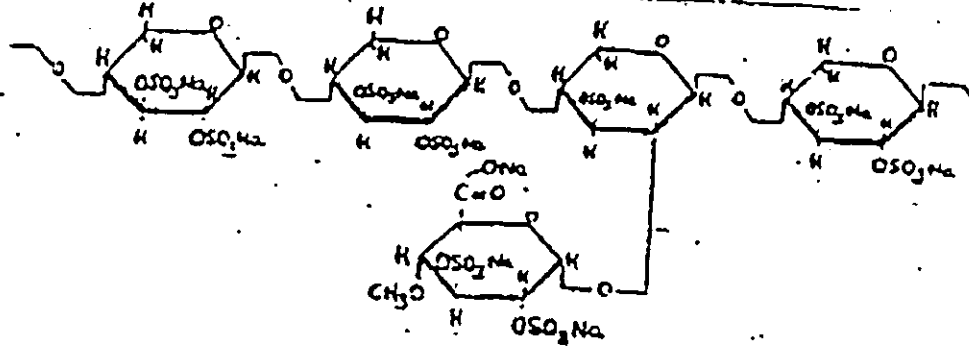
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Pentosan polysulfate sodium

Description

Pentosan polysulfate sodium is a sulfated polysaccharide with an average molecular weight between 4000 and 6000 Daltons. The structure of the polymer is composed of (1 → 4) linked β-D-xylopyranose residues with approximately every tenth D-xylopyranose residue carrying (through position 2) a single 4-O-methyl-D-glucuronic acid (= carboxy pentose) residue attached as side chain.

Structural formula



Therapeutic claim

Antithromboticum, fibrinolyticum.

Also classified as an orphan drug for the treatment of interstitial cystitis.

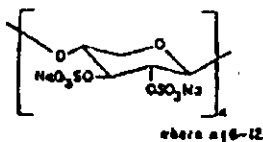
Manufacturer

000035

1994 USP Dictionary of USAN and International Drug Names

Pentosan Polysulfate Sodium

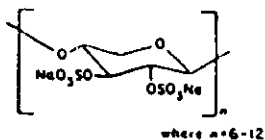
Pentosan Polysulfate Sodium [1988] (pen' toe san pol i sul' fate). $[C_5H_6Na_2O_{10}S_2]_n$ ($n = 6$ to 12). 6000.00. [Pentosan Polysulphate Sodium is BAN.] (1) β -D-Xylan, (1 $\rightarrow$ 4), 2,3-bis(hydrogen sulfate), sodium salt; (2) (1 $\rightarrow$ 4)- β -D-Xylan 2,3-bis(hydrogen sulfate), sodium salt. CAS-116001-96-8. INN. *Anti-inflammatory (interstitial cystitis)*. $\diamond$ SP54; PZ68



1995 USP Dictionary of USAN and International Drug Names

Pentosan Polysulfate Sodium

Pentosan Polysulfate Sodium [1988] (pen' toe san pol i sul' fate). $[C_5H_6Na_2O_{10}S_2]_n$ ($n = 6$ to 12). [Pentosan Polysulphate Sodium is BAN.] (1) β -D-Xylan, (1 $\rightarrow$ 4), 2,3-bis(hydrogen sulfate), sodium salt; (2) (1 $\rightarrow$ 4)- β -D-Xylan 2,3-bis(hydrogen sulfate), sodium salt. CAS-116001-96-8. INN. *Anti-inflammatory (interstitial cystitis)*. $\diamond$ SP54; PZ68



4

Material Safety Data Sheet
May be used to comply with
OSHA's Hazard Communication Standard,
29 CFR 1910.1200. Standard must be
consulted for specific requirements.

U.S. Department of Labor
Occupational Safety and Health Administration
(Non-Mandatory Form)
Form Approved
OMB No. 1218-0072



IDENTITY (As Used on Label and List)
Pentosan Polysulfate Sodium (PPS)

Note: Blank spaces are not permitted. If any item is not applicable, or no information is available, the space must be marked to indicate that.

Section I

Manufacturer's Name bene-Arzneimittel GmbH	Emergency Telephone Number n/a
Address (Number, Street, City, State, and ZIP Code) Herterichstr. 1	Telephone Number for Information (089) 79 20 41
8000 München 71	Date Prepared Feb. 8, 1992
Germany	Signature of Preparer (optional)

Section II — Hazardous Ingredients/Identity Information

Hazardous Components (Specific Chemical Identity; Common Name(s))	OSHA PEL	AOIH TLV	Other Limits Recommended	% (optional)
PPS is $(C_5H_6O_3(O^-\text{SO}_3^-Na)_2)_n$ with n between 6 and 12				
a polymer xylose sugar chain with sulfated hydroxyl groups, sodium salt				
No hazardous ingredients				

Section III — Physical/Chemical Characteristics

Boiling Point n/a	Specific Gravity (H ₂ O = 1) apx. 4
Vapor Pressure (mm Hg) n/a	Melting Point 170°C, decomp.
Vapor Density (AIR = 1) n/a	Evaporation Rate (Butyl Acetate = 1) n/a
Solubility in Water 7 g in 10 ml	
Appearance and Odor White to faintly yellow powder, odorless	

Section IV — Fire and Explosion Hazard Data

Flash Point (Method Used) n/a	Flammable Limits n/a	LEL n/a	UEL n/a
Extinguishing Media water			
Special Fire Fighting Procedures n/a			
Unusual Fire and Explosion Hazards not known			

000037

Section V — Reactivity Data

Stability	Unstable		Conditions to Avoid temperatures higher than 80°C
	Stable	X	

Incompatibility (Materials to Avoid)

Acids

Hazardous Decomposition & Byproducts

Sulfuric acid vapors

Hazardous Polymerization	May Occur		Conditions to Avoid
	Will Not Occur	X	

Section VI — Health Hazard Data

Route(s) of Entry:	Inhalation?	Skin?	Ingestion?

n/a

Health Hazards (Acute and Chronic)

Inhalation of large amounts could lead to bleeding;
after ingestion of large amounts internal bleeding is possible;
after continual intake of 3 g MDI loss of hair

Carcinogenicity:	NTP?	IARC Monographs?	OSHA Regulated?
	not known	not known	none

Signs and Symptoms of Exposure

Medical Conditions

Generally Aggravated by Exposure

coagulation problems in patients with haemophilia may be aggravated

Emergency and First Aid Procedures

Monitoring of coagulation parameters, administration of protamine sulfate

Section VII — Precautions for Safe Handling and Use

Steps to Be Taken in Case Material is Released or Spilled

wash away with water

Waste Disposal Method

no special precautions

Precautions to Be Taken in Handling and Storing

Store in a dry place at room temperature,
avoid temperatures above 80°C

Other Precautions

n/a

Section VIII — Control Measures

Respiratory Protection (Specify Type)

If dusts are generated, a dust mask is to be worn

Ventilation	Local Exhaust	recommended	Special
	Mechanical (General)		Other
Protective Gloves	recommended	Eye Protection	chemical goggles
Other Protective Clothing or Equipment	n/a		
Work Hygienic Practices	n/a		

000038

5



8800 Northwest 36th Street
Miami, Florida 33178-2404
Telephone 305/590-2200
Facsimile 305/590-2252

MATERIAL SAFETY DATA SHEET

Identity (Product Name): Elmiron Capsules 100 mg.

Date Prepared: March 24, 1995

Section I. Identification

Manufacture's Name : Baker Norton Pharmaceuticals, Inc.
Address : 8800 NW 36 Street, Miami, FL 33178
Emergency Telephone No. : (305) 590-2254
Information Telephone No. : (305) 590-2200

Section II. Hazardous Ingredients

<u>Common Name</u>	<u>OSHA PEL</u>	<u>ACGIH TLV</u>	<u>%</u>
None	NA	NA	NA

Section III. Physical/Chemical Characteristics

Boiling Point : NA Solubility in water: Low
Vapor Pressure : NA Specific Gravity : NA
Vapor Density : NA pH : NA
Appearance and Odor: White opaque gelatin capsule.

Section IV. Fire and Explosion Hazard Data

Non-flammable or combustible material.
Flash Point: > 200 F

Section V. Reactivity Data

Stable. Store at room temperature.

Section VI. Health Hazard Data

No recognizable health hazard data.

000039

Section VII. Precautions for Safe Handling and Use

Spill or Leak Procedures: Normal clean up and wash down with hot water. Dispose of following pertinent federal, state, or local regulations.

Section VIII. Control Measures

First Aid Procedures:

Eyes : irrigate the eye immediately with water for five minutes.

Skin : NA

Ingestion : Ingest large quantities of fluid, preferably water. Induce vomiting if large amounts are ingested. Contact the Poison Center for additional information, if required.

Respiratory Protection: NA

Protective Clothing : NA

Eye Protection : NA

16

Metabolism and Pharmacokinetics of Sodium Pentosan Polysulphate

Stowe School Symposium on Drug Metabolism
April 8-11, 1984 - Buckingham

000041

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Greenlade D., Vickers J.A., Hopkins R., Ward J., Halse T.

ABSTRACT

Sodium pentosan polysulphate (SP 54) is a sulphated polysaccharide used in the treatment of thrombosis and interstitial cystitis.

When randomly tritiated SP 54 was given orally to rats (10 mg/kg) and healthy male volunteers (2-10 mg/kg), the majority of radioactivity (85.1-89.6%) was voided in faeces with 3.4-5.3% being renally eliminated. Plasma radioactivity in the rat peaked at 0.5 hr post-dose and then declined rapidly, whereas in man peak levels were maintained between 1 and 4 hr post-dose. A triexponential decline in plasma radioactivity was observed in rats given intravenous (^3H)-SP 54 (0.025-0.5 mg/kg).

There was negligible renal elimination of (^3H)-SP 54 in man, most of the radioactivity being associated with short chain and probably desulphated fragments.

Following chronic administration of (^3H)-SP 54 to the rat, the relative proportion of renally eliminated radioactivity represented by parent drug increased from 6.3 (Day 1) to 15.1% (Day 13).

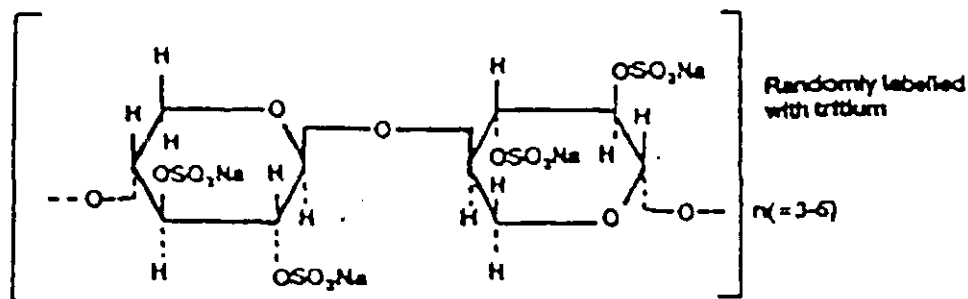
OBJECTIVES

(I) To examine the metabolism and pharmacokinetics of orally administered (^3H)-SP 54 in man.

(II) To study the metabolism of (^3H)-SP 54 when given either intravenously or orally to the rat.

INTRODUCTION

Sodium pentosan polysulphate (SP 54) is related to a group of anionic macromolecules that includes heparins and chondroitin sulphates. It is a linear macromolecule made up of sulphated (1 to 4) linked β -D-xylopyranose units (I). Randomly tritiated SP 54 was prepared by catalytic exchange using tritium gas. There was no significant loss of tritium label from purified (^3H)-SP 54 in any of the biological systems used.



000042

METHODS

Sprague Dawley pigmented rats of both sex were administered a single oral dose (10 mg/kg aq. solution) of (³H)-SP 54. The absorption, tissue distribution and excretion of radioactivity were examined up to 168 hr post-dose.

The metabolism of (³H)-SP 54 and the accumulation of drug related material in the endothelium of the aorta, vena-cava, and bladder of male rats given 14 consecutive single daily doses of drug (10 mg/kg) were also examined.

Specimens of urine collected over 24 hr following the 1st, 3rd, 7th and 13th doses of (³H)-SP 54 were analysed by gel-permeation chromatography.

The pharmacokinetics of non-volatile radioactivity were studied in male rats given a single intravenous dose of (³H)-SP 54 (0.025, 0.05, 0.10, 0.50 mg/kg).

Three healthy male volunteers were administered a single oral dose (capsule) of (³H)-SP 54 at a dose level of 2, 5 or 10 mg/kg body weight. Serial samples of blood, urine and faeces were collected for 120 hr post-dose. The nature of metabolites in the urine (0-24 hr) of subject 1M was examined by gel-permeation chromatography.

RESULTS

Within 48 hr of a single oral dose of (³H)-SP 54 to the rat and man, most of the administered radioactivity had been voided in faeces with little renal elimination. In rat, there was a wide tissue distribution of radioactivity, the highest residue (0.063% of the dose) being found in liver at 168 hr post-dose.

Plasma concentrations of non-volatile radioactivity in the rat peaked at 0.5 hr post-dose, and thereafter declined rapidly. In man, peak concentrations occurred at 1 hr and generally remained at this level until 4 hr post-dose. No non-volatile radioactivity was detected in the post-8 hr samples.

Following intravenous administration of (³H)-SP 54 to the rat, plasma concentrations of radioactivity declined triexponentially, similar AUC's (normalised for dose) and half-lives being found at all dose levels.

(³H)-SP 54 was extensively metabolised, negligible quantities of parent drug being found in the urine of subject 1M. On chronic administration of (³H)-SP 54 to the rat, the percentage of urinary radioactivity associated with unchanged drug increased from 6.3% (Day 1) to 15.1% (Day 13). Concentrations of radioactivity in the endothelium of the aorta, vena-cava and bladder after the 1st and 14th doses were similar, levels being either very low or below the limit of detection.

TABLE I

Elimination of radioactivity following oral administration of (³H)-SP 54

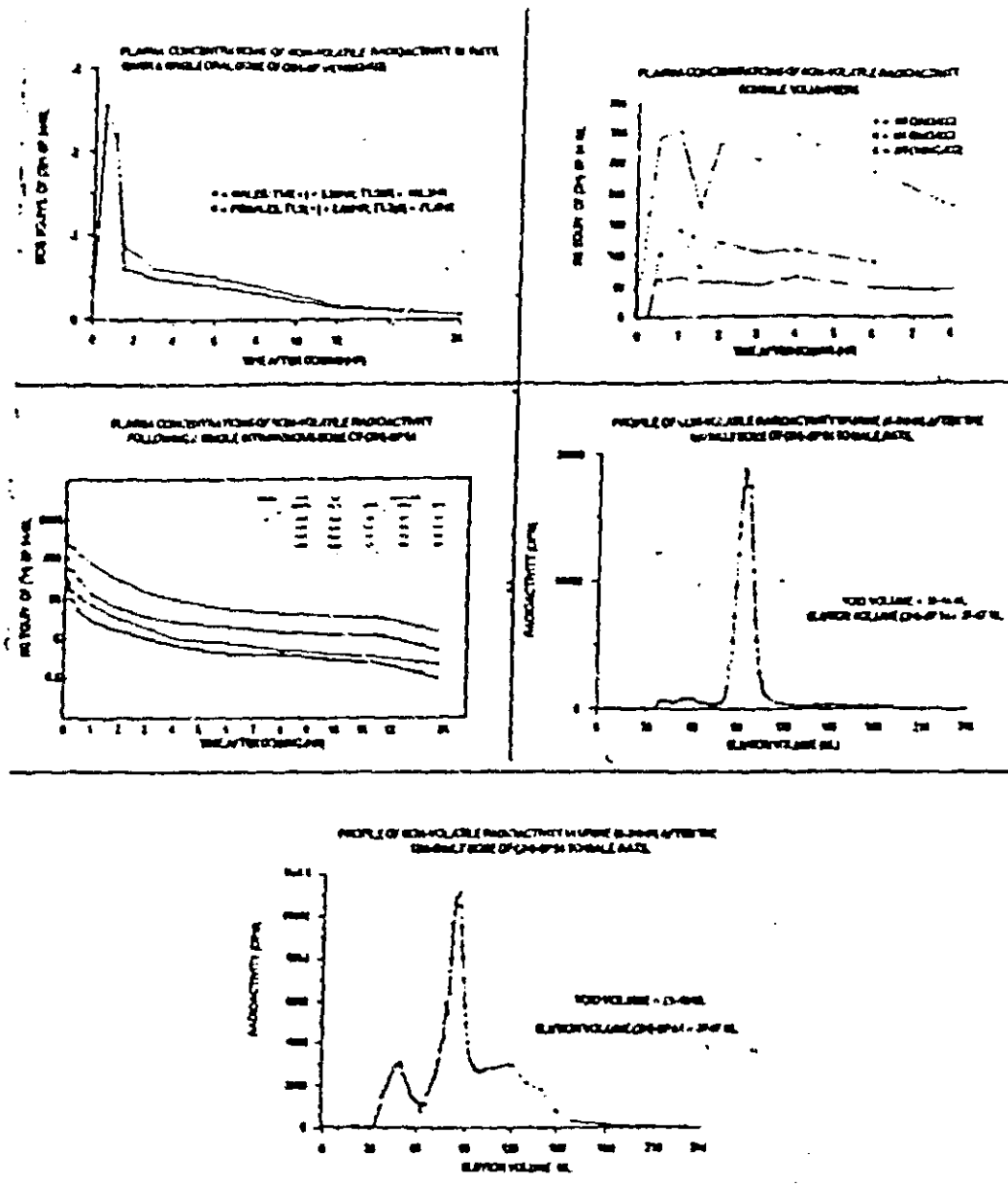
Excreta	Rat (n = 6)		Man (n = 3)		
	Male(3)	Female(3)	1M(2 mg/kg)	2M(5 mg/kg)	3M(10 mg/kg)
Urine	5.3	4.4	3.4	3.5	3.5
Faeces	88.6	88.5	86.9	86.9	87.4
Carcass	0.1	0.1	N/A	N/A	N/A
Total	95.0	93.0	70.3	90.4	90.9

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NDA 28-193

6 OF 7



DISCUSSION

In both rat and man the low renal elimination of radioactivity may, in part, be due to biliary elimination, but more probably reflects the low bioavailability of (^3H) -SP 54 and/or its metabolites after oral administration. The difference in the plasma radioactivity/time curves between rat and man may be a consequence of the differences in the formulation of (^3H) -SP 54 used.

The similar plasma half-lives and AUC values (normalised for dose) observed in the rat after intravenous administration suggested that the pharmacokinetics of (^3H) -SP 54 did not vary over a dose range of 0.025-0.5 mg/kg. Previous studies with heparin in dog and man have demonstrated that plasma half-lives of heparin, as determined by bioassay, were dose dependent.

In both species (^3H) -SP 54 was extensively metabolised, virtually all of the radioactivity in urine being present as short chain and possibly desulphated fragments. The increase in renal elimination of unchanged (^3H) -SP 54 in rat chronically administered the drug suggested that there was a change in its disposition.

The antithrombotic properties of heparin are thought to arise from its accumulation in vascular cell walls. There was little evidence for an accumulation of non-volatile radioactivity in tissue endothelia of the rat after chronic administration of (^3H) -SP 54.

7

JIM 05805

The production of antibodies to pentosanpolysulfate (ELMIRON, SP-54)

Hugh J. Callahan¹, Dolores Shupp-Byrne¹, Melina Pizzo¹, C. Lowell Parsons²
and S. Grant Mulholland¹

¹ Department of Urology, Thomas Jefferson University, Philadelphia, PA, U.S.A., and ² University of California, San Diego, CA, U.S.A.

(Received 17 August 1990, revised received 24 September 1990, accepted 25 September 1990)

Pentosanpolysulfate (PPS) represents the product obtained after sulfation of xylan and is composed of β 1 $\rightarrow$ 4-D-xylopyranose residues sulfated at C2 and C3. Studies have shown that this compound can often be effective in relieving the symptoms of interstitial cystitis (IC). In order to elucidate the mode of action of PPS in IC, a sensitive and reliable assay was needed. To this end we prepared an immunogenic form of PPS by coupling it to methylated bovine serum albumin (MBSA). This complex was used to immunize NZW rabbits (1 mg, IM). Four of five animals responded with anti-PPS antibodies, three of which had high titer ($> 1/2000$) as measured by an enzyme-linked immunosorbent assay (ELISA). All sera were routinely absorbed with an MBSA-Sepharose immunoabsorbent to remove anti-MBSA antibodies. ELISA inhibition tests were used to determine the sensitivity and specificity of the sera. At least 50 ng/ml of PPS could be routinely detected by this assay. A number of naturally occurring proteoglycans, polysaccharides, monosaccharides and disaccharides were examined for reactivity with the antibodies but only heparin was an effective inhibitor. Absorption with heparin immunoabsorbents reduced, but did not eliminate, the ability of heparin to inhibit anti-PPS binding. This activity could be destroyed by treatment with heparinase without affecting PPS inhibition.

Normal urine did not affect the ELISA or ELISA inhibition tests and thus allowed the determination of PPS levels in IC patient urines. Initial analysis of seven IC patients receiving oral PPS revealed urine concentration of 0.8–16.0 μ g/ml. No inhibition could be detected in pre-treatment urine samples.

Key words: Pentosanpolysulfate; ELISA; Interstitial cystitis

Introduction

One of the more promising treatments being examined to relieve the symptoms associated with interstitial cystitis (IC) is the administration of the semi-synthetic oligosaccharide ELMIRON, also

known as SP-54 or pentosanpolysulfate (PPS). This compound represents the product obtained after sulfation of a naturally occurring xylan. Chemically it is composed of β 1 $\rightarrow$ 4-xylopyranose residues sulfated at positions C2 and C3. PPS has been reported to have a higher fibrinolytic potentiating activity than heparin in addition to a significant thrombolytic effect in experimental animals (Tangen and Julin, 1983). Pharmacokinetic data suggest that after intravenous administration of ³⁵S-PPS the kidneys show the greatest

Correspondence to: H.J. Callahan, Department of Urology, Thomas Jefferson University, 1075 Walnut Street, Philadelphia, PA 19107-5084, U.S.A.

localization with lesser amounts in the liver, lung, skin and periosteum. In addition these investigators claim that sodium pentosanpolysulfate is desulfated before entering the urine. Odland et al. (1987) have shown that tritiated PPS preferentially localizes in the urinary tract of rats. Four hours after oral administration, most of the compound appeared to be in the large intestine with some localization to the liver, kidney, ureter and urinary bladder.

Using a rabbit model of induced bacterial cystitis, which involved weak acid treatment to remove the bladder's mucosal layer, Parsons et al. (1980) have shown PPS to be quite efficient in restoring the natural antibacterial properties of this organ. Other studies by these investigators have led them to hypothesize that sulfated polysaccharides or glycosaminoglycans on the luminal surface of the bladder represent the primary defense mechanism against insults from the noxious elements of urine including pathogenic microorganisms, carcinogen and other low molecular toxic compounds (Parsons et al., 1985; Parsons, 1986).

Recent clinical trials (Parsons and Mulholland, 1987; Lilly and Parsons, 1989) have indicated that oral administration of PPS may be efficacious in relieving the symptoms associated with interstitial cystitis in a population of female patients with mild to moderate disease, but little data is available concerning the urine and/or serum levels in patients receiving therapy. This is primarily due to the lack of a sensitive assay for this compound. With this in mind we have developed an enzyme immunoassay which can be used to monitor low levels of the drug in body fluids. In this report we describe the methodology employed to raise antibodies to PPS, their specificity and performance in analyses with I.C. patient urine samples.

Materials and methods

Chemicals

All chemicals were A.C.S. grade or superior. PPS was obtained from BeneChemie (Munich, F.R.G.) and Sigma Chemical Co. (St. Louis, MO). Column chromatographic supports were purchased from Bio-Rad (Rockville Centre, NY) and Pharmacia (Piscataway, NJ). The following were from

Sigma Chemical Co.: glucuronic acid, galacturonic acid, *N*-acetyl galactosamine, glucosamine-2-sulfate, 3-sulfate, 6-sulfate, 2,3-disulfate, 2,6-disulfate, polygalacturonic acid, α -1 acid glycoprotein, bovine glycoprotein, hyaluronic acid, xylan, heparin, heparin sulfate, chondroitins A and C, dextran, heparin-agarose, heparin-acrylic and heparinase II. Bovine serum albumin (BSA) and methylated bovine serum albumin (MBSA) were coupled to Sepharose 4B-CL (Pharmacia) via the cyanogen bromide procedure. (Stefanelli et al., 1990)

Rabbits and immunizations

NZW rabbits (3 kg) were purchased from Ace (Boyertown, PA). Immunogenic complexes of PPS were prepared as follows: a solution of 1% MBSA dissolved in water was slowly added to a 1% aqueous PPS solution with stirring. After 30 min the aggregate was centrifuged (2000 rpm, 20 min) and washed with phosphate-buffered saline (PBS) containing 0.1 M NaCl, 1.5 mM phosphate, pH 7.2. For initial immunizations the MBSA-PPS complex (2 mg/ml) was homogenized with an equal volume of complete Freund's adjuvant (FCA) and injected IM (1 mg/rabbit). The animals were bled and boosted in incomplete Freund's adjuvant (FIA) every 2-3 weeks. Sera were tested for antibody production by ELISA, both neat and after BSA-MBSA immunoadsorbent absorption. Normal rabbit serum was prepared from unimmunized animals.

Immunoabsorbent treatment of antisera was done by adding an equal volume of gel (packed by centrifugation at 10,000 rpm for 5 min) to the undiluted antiserum. After mixing overnight at 4°C the gel was separated from the serum by centrifugation and washed repeatedly with PBS. Before use, all absorbed sera were filtered (0.2 μ m) to remove any traces of residual gel.

Enzyme-linked immunosorbent assay (ELISA)

Microtiter plates (Immunolon II, Dynatech) were coated for 60 min (0.1 ml/well) with poly-L-lysine (100 μ g/ml) diluted in 0.01 M NaHCO₃ buffer pH 9.6 with 0.02% NaN₃. The plates were washed three times in PBS and PPS added (100 μ l/well of a 5 μ g/ml solution) incubated at 4°C on a rocking platform for 18 h and then washed

ten times with 0.05 M PBS, pH 7.4 containing 0.02% NaN₃ 0.05% Tween 20 and 1% normal goat serum to avoid nonspecific adsorption (PBS-Tween NGS). Antiserum dilutions were prepared in PBS-Tween NGS) and then added to each antigen coated well. As a control, antiserum was also added to wells which had been coated with rabbit serum albumin. The plates were rocked at 37°C for 60 min, again washed ten times with PBS-Tween, and excess alkaline phosphatase conjugated goat anti-rabbit immunoglobulin in PBS-Tween was added. Enzyme substrate was prepared by dissolving one tablet (5 mg) of *p*-nitrophenyl phosphate (Sigma) in 5 ml of 10% diethanolamine buffer which had been warmed to room temperature. Diethanolamine buffer was made in the following way: 97 ml of diethanolamine (Fisher, Fair Lawn, NJ), 100 mg of MgCl₂ · 6H₂O and 0.2 g NaN₃ were dissolved in 800 ml of water. This buffer was stored at 4°C in the dark. The enzyme substrate reaction was monitored by absorption at 405 nm after 15, 30, 45 and 60 min. in a Titertech Multiscan. Inhibition of antigen binding was done by pre-incubating various concentrations of inhibitor with primary antibody for 1 h, then continuing the assay as above. The percent inhibition was calculated from the following equation:

$$\% \text{ inhibition} = \left(1 - \frac{\% \text{ bound with inhibitor}}{\% \text{ bound without inhibitor}} \right) \times 100$$

Chemical and physical analyses

Ultraviolet and visible absorption data were obtained on a Cary 14 or Varian DMS80 spectrophotometer. PPS concentrations were estimated from absorbance measurements at 220 and 260 nm with extinction coefficients determined in our laboratory using dry weight measurements. Antisera concentrations were estimated from absorbances at 280 nm.

Patients

IC patients were diagnosed according to the criteria developed by the NIH Workshop on Interstitial Cystitis. (Gillenwater and Wein, 1988) Urine samples were obtained prior to PPS and administration and at various times after treatment. Nor-

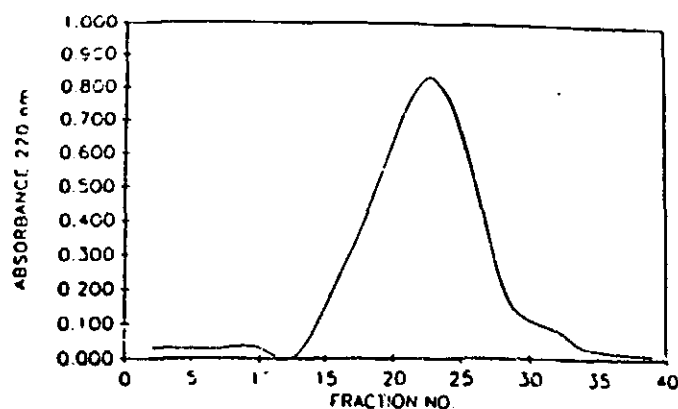


Fig. 1. PPS chromatographed on Sephadex G-50. A 2% solution in 0.1 M NaCl was applied to a 0.9 cm × 57 cm column and eluted with 0.1 M NaCl.

mal urine specimens were obtained from department personnel.

Results

When chromatographed on Sephadex G-50 or BioGel P-6 the PPS eluted as a single peak (Fig. 1), the breadth of which would indicate some polydispersity. Using proteins as molecular weight markers the average molecular weight was estimated to be approximately 5000.

The ultraviolet absorption spectrum was as expected for PPS samples obtained from Sigma Chemical Company, however, one of two samples from BeneChemie demonstrated an unusually high absorbance at 260 nm (Fig. 2). This was apparently due to pyridine molecules which cova-

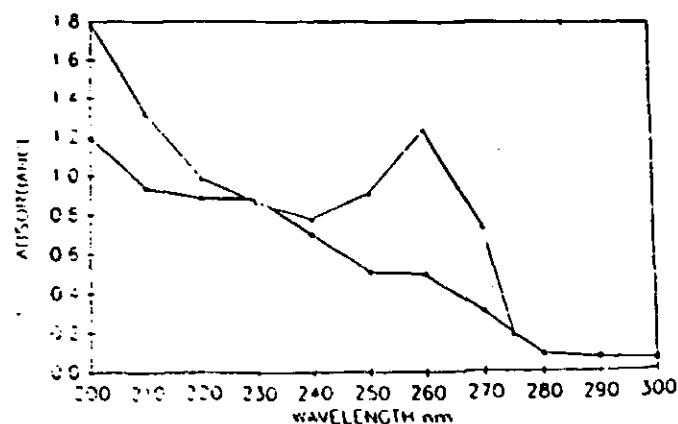


Fig. 2. Ultraviolet absorption spectrum of PPS samples. ---: from Sigma Chemical Co.; ▲—▲: from Bene-Chemie.

lently attached to the PPS during synthesis. This modification does not affect its clinical properties (personal communication Dr. E.A. Schauburg, BeneChemie, and Muholland et al. (1990), which reports no unusual side effects).

The extinction coefficients were as follows: for the BeneChemie sample, $E_{1\text{ cm}}^{1\%} = 6.15$ (260 nm) and 4.99 (220 nm); for the Sigma sample: $E_{1\text{ cm}}^{1\%} = 2.02$ (260 nm) and 3.67 (220 nm).

After repeated immunization (four of five rabbits responded with a high titer to PPS (1/2000 or greater before absorption) while one developed antibodies to MBSA only. All of the PPS positive sera were absorbed with both BSA-Sepharose and MBSA-Sepharose. After absorption none of the antisera reacted with MBSA. However some did react very weakly with heparin coated plates. These were treated with heparin-agarose and heparin-acrylic gels until there was no measurable binding to heparin in direct ELISA tests. This is shown in Fig. 3 for one antiserum which had been extensively absorbed (and thus diluted).

ELISA inhibition tests with the proteoglycans listed in the material and methods section were negative with the exception of heparin. Several proteoglycans exhibited 5–15% inhibition at very high concentrations (500 $\mu\text{g}/\text{ml}$) but were ineffective at lower concentrations. None of the mono- or disaccharides inhibited at concentrations of 500 $\mu\text{g}/\text{ml}$. Surprisingly heparin was still inhibitory after two absorptions of the sera with the immunoabsorbents (Fig. 4). Although demonstrating less than 1% of the activity of PPS at the 50%

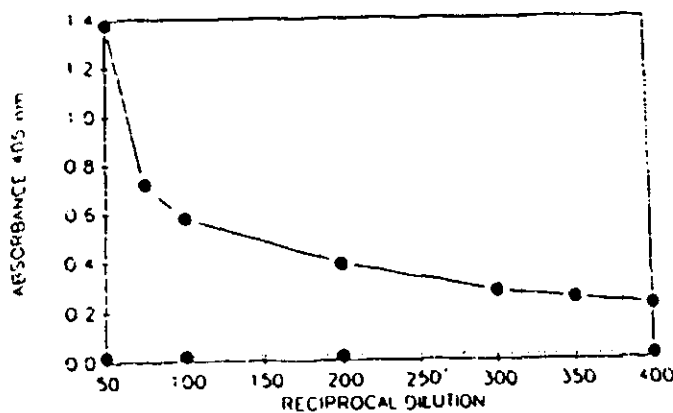


Fig. 3. ELISA of anti-PPS serum. Antiserum had been absorbed with BSA, MBSA and heparin immunoabsorbents. Plates were coated with PPS (●—●) or heparin (○- - -○).

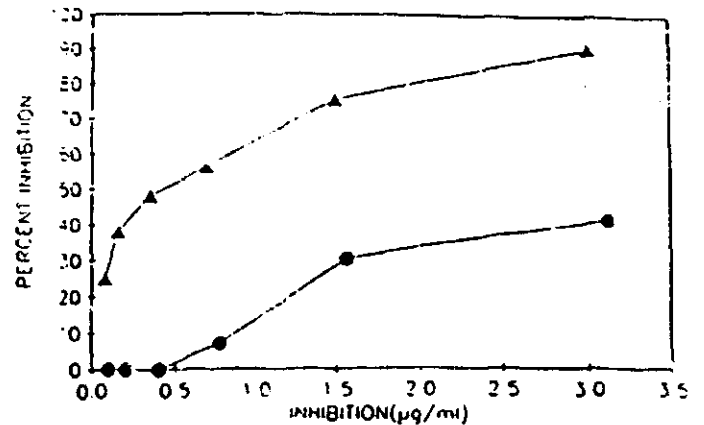


Fig. 4. ELISA inhibition. Plates were coated with PPS. After treatment with the immunoabsorbents listed in Fig. 3, aliquots of the serum were incubated with inhibitors and then added to the plates (see text). Δ — Δ : PPS; $\bullet$ — $\bullet$: heparin.

inhibition level, this reactivity could not be removed with repeated absorptions.

PPS was a very effective inhibitor of the antisera whether dissolved in PBS or normal urine. It produced 50% inhibition at 0.4 $\mu\text{g}/\text{ml}$ and 25% inhibition at 0.05 $\mu\text{g}/\text{ml}$ in both solvents (Fig. 4). Heparin inhibited less effectively: 25% at 1.5 $\mu\text{g}/\text{ml}$ and 40% at 3.0 $\mu\text{g}/\text{ml}$.

Since the heparin inhibition could possibly be a complication in identifying or quantitating PPS levels in patients a method of differentiating the two substances was needed. To this end we used heparinase digestion of both PPS and heparin. The results of these treatments are shown in Table I. There was a significant loss of heparin inhibi-

TABLE I

EFFECT OF HEPARINASE TREATMENT ON THE SEROLOGICAL ACTIVITY OF SP-54 AND HEPARIN

Enzyme	Substrate	% Inhibition ($\mu\text{g}/\text{ml}$) ^a	A_{235} (mg/ml)
Heparinase (In) ^b	SP-54	99 (5)	0.320
	SP-54	92 (1)	
Heparinase	SP-54	99 (5)	0.318
	SP-54	92 (1)	
Heparinase (In)	Heparin	91 (25)	0.032
	Heparin	82 (5)	
Heparinase	Heparin	25 (25)	4.580
	Heparin	13 (5)	

^a Inhibition of ELISA (see text).

^b In: heparinase inactivated by heating.

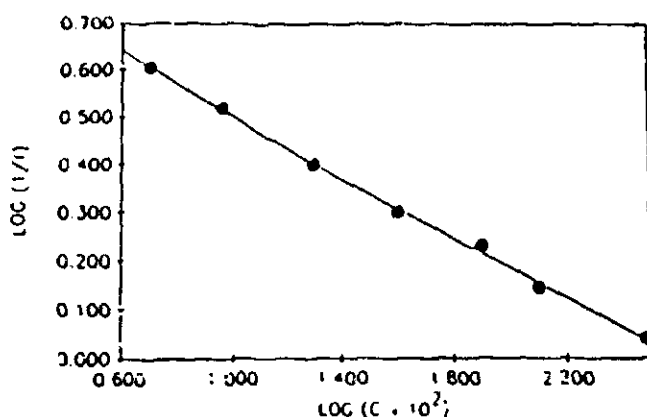


Fig. 5. Standard inhibition graph used with patient samples. f is the fractional inhibition and C is the concentration of PPS in $\mu\text{g}/\text{ml}$ of PBS or normal urine.

tory activity after one treatment (82% reduced to 13%). However, this enzyme had no effect on the serological activity of the PPS. The table also provides spectroscopic evidence of the heparinase activity. The absorbance at 235 nm is an approximation of the degree of digestion since heparinase treatment produces an unsaturated bond between C4 and C5 in the uronic acid residues. It is apparent that PPS is not digested with the enzyme since there is no change in absorbance. On the other hand the absorbance of the treated heparin is 140 times greater than the untreated.

For the analysis of the patient urines, the inhibition data obtained with PPS was converted to a form similar to a Langmuir adsorption isotherm (Callahan et al., 1971) in which the coordinates were $\log(\text{concentration} \times 100)$ vs. $\log(1/f)$ where

TABLE II
PPS LEVELS IN PATIENT URINES BEFORE AND AFTER ORAL ADMINISTRATION

Patient	Urine concentration ($\mu\text{g}/\text{ml}$) ^a	
	Pre	Post
1	0	0.8
2	0	1.2
3	0	1.2
4	0	5.8
5	0	16.0
6	0	1.0
7	0	3.4

^a Determined by ELISA inhibition.

f is the fractional inhibition (i.e., 5 inhibitions divided by 100) This format allows the calculation of inhibitor concentrations from the fractional inhibition using the mathematical description of a straight line (Fig. 5) and was accurate between 25% and 90% inhibition (50 ng–3 μg PPS).

Table II shows the levels of PPS found in the urine of seven IC patients before and after oral administration of the polysaccharide. There was no detectable PPS in any pretreatment urines while post-treatment levels ranges from 0.8 to 15 $\mu\text{g}/\text{ml}$ urine.

Discussion

Several groups of investigators have done clinical trials of PPS in IC patients (Holm-Bentzen et al., 1987; Parsons and Mulholland, 1987; Lilly and Parsons, 1989). The results of these studies have been equivocal at best. This is probably due to a number of factors, including a lack of uniformity in both diagnostic criteria and the stage of disease at entry into the trials. With the application of the NIH guidelines for the diagnosis of IC in research subjects it has become apparent that PPS has an effect in ameliorating the disease symptoms in the earlier stages of IC but not in the late stages (Mulholland et al., 1990). In these studies no accurate assessment of urinary or blood levels of PPS was made since chemical analysis for this compound is laborious and time consuming.

Using techniques which were successful in raising antibodies to synthetic polypeptides (Liberti et al., 1974) we have produced anti-PPS antibodies in four of five rabbits. Some of these antisera also contained antibodies to MBSA and heparin, however, after absorption with suitable immunoadsorbents there was no direct binding to these compounds as measured by ELISA tests. However, using ELISA inhibition tests, heparin demonstrated considerable inhibition of anti-PPS binding to PPS coated plates.

The mechanisms responsible for these anomalous results are not immediately apparent. However, two possible explanations could be invoked. (1) The observed inhibition is a non-specific result of the high negative charge density of heparin

which might interfere with the physicochemical interactions between antibody and PPS.

- (2) The chemical procedure by which heparin is coupled to agarose or acrylic beads may disrupt the conformational structures of the heparin molecule to such an extent that it cannot react with the antibodies. Thus these immunoabsorbents would not be able to remove some of the antibodies reactive with intact heparin.

Explanation 1 seems unlikely since a number of negatively charged proteoglycans and sulfated sugars gave no inhibition in this system. In addition, heparin did not inhibit the MBSA-anti-MBSA reaction at concentrations of 500 $\mu\text{g}/\text{ml}$ (data not shown). Explanation 2, on the other hand, is a valid possibility although difficult to prove conclusively. There are numerous examples of systems which require that an antigen have an intact three dimensional structure in order to react with antibody. These include polypeptide (Callahan et al., 1975), polysaccharide (Callahan and Maurer, 1975) and nucleic acid antigens (Callahan and Maurer, 1979). It also has been reported that coating of some antigens onto plastic results in a loss of native structure Darst et al. (1988) which could explain the lack of binding of the absorbed anti-PPS sera to heparin coated plates (Fig 3). This phenomenon has not been investigated further since the heparinase experiments have shown that it is possible to differentiate PPS from heparin in ELISA studies.

In developing a method for the quantitative analysis of PPS, urine samples were obtained from numerous normal donors. None inhibited the ELISA tests to any significant degree. Thus standard curves were constructed using PPS dissolved in urine. The format used was linear between 25% and 90% inhibition. As is to be expected, the slope of such a curve is dependent upon the antibody concentration of the serum. However, when diluted to a concentration which allows equal binding in ELISA, the inhibition is the same.

The gel filtration studies suggest that PPS has an average molecular weight of 5000, although this is tentative since proteins were used as markers. However, this value is close to that obtained by others (Odlind et al., 1987). There were no unique spectral properties, except for the sample with the

high 260 nm absorbance. The differences between the extinction coefficients of the samples can be explained by the pyridine residues of the serum.

In summary, we have shown that antibodies can be raised in rabbits to PPS. Though a population of these antibodies can cross react with heparin, it is possible to differentiate between PPS and heparin by heparinase treatment. An ELISA inhibition assay has been developed for PPS which can detect as little as 50 ng/ml of PPS in the presence of urine. This assay should be useful for monitoring both urinary and blood levels of PPS. PPS is currently being administered at levels dictated by the subjective responses of the individual patient. It may now be possible to determine the blood and urine levels which are optimum for relief of symptoms. However, the greatest potential utility of these antisera may be in defining the mechanism of action of PPS in IC. It should be possible to determine whether this compound acts by binding to the urothelium and repairing permeability defects or by other mechanisms such as inducing increased secretion of urinary tract proteoglycans. Such studies could significantly advance our knowledge of the etiology of this disease.

Acknowledgements

The authors gratefully acknowledge the technical assistance of Mr. Abram Kaufman and Mr. Robert Fritz.

This work was supported in part by grants from the NIH (1R01DK38895) and the National Kidney Foundation.

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8800 Northwest 36th Street
Miami, Florida 33178-2404
Telephone 305/590-2200
Facsimile 305/590-2252

Environmental Compliance Statement

Baker Norton Pharmaceuticals, Inc. states that is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Elmiron® at its facilities at 8800 Northwest 36th Street, Miami, Florida 33178-2404 as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Elmiron® at its facilities at 8800 Northwest 36th Street, Miami, Florida 33178-2404.

A handwritten signature in black ink, appearing to read 'Alfredo Delregato', is written over a vertical line that extends down to the printed name below.

Alfredo Delregato
Safety & Environmental Manager
Baker Norton Pharmaceuticals, Inc.

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METROPOLITAN DADE COUNTY, FLORIDA



LIQUID WASTE
ANNUAL OPERATING PERMIT

ENVIRONMENTAL RESOURCES MANAGEMENT
POLLUTION PREVENTION DIVISION
SUITE 800
33 S.W. 2nd AVENUE
MIAMI, FLORIDA 33130-1540
(305) 372-6817

PERMITTEE:
Mr. Bob Hely
BROWNING-FERRIS INDUSTRIES OF FL
2380 COLLEGE AVE
DAVIE, FL 33317

PAGE 1 OF 1
PERMIT No.: LW-00254-95 (BW) BW 00
SOURCE NAME: BROWNING FERRIS IND. OF FL INC.
LOCATION: 7724 NW 64 ST
MIAMI, FL 33166

DESCRIPTION OF FACILITY/EQUIPMENT:

This document, issued under the provisions of Chapter 24, Metropolitan Dade County Code (Dade County Environmental Protection Ordinance), shall be valid from April 01, 1995 through March 31, 1996. The above named permittee, is hereby authorized to operate as a Liquid Waste Transportation business from the above location, and with the equipment bearing the following identifying stickers:
BW95-254-001 through BW95-254-017

Subject to conditions (1) through (18) listed below and in the following pages (if any) of this document.

SPECIFIC CONDITIONS:

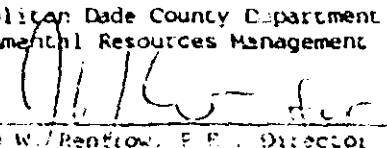
- 01 Correctly completed monthly reporting forms and corresponding fees are required to be submitted to DERM on/or before the 10th of the following month.
- 02 No waste other than biohazardous waste shall be transported under this permit.
- 03 All containers, bags and vehicles used for the transport of biohazardous waste shall be properly maintained and operated in order to preclude any leaking, spills, etc. A satisfactory method of secondary containment shall be utilized. Any primary container which leaks shall be repackaged immediately.
- 04 All biohazardous waste will be incinerated or properly treated before disposal at an approved landfill.
- 05 Trucks shall be disinfected on a routine basis. Within 30 days of receipt of this document, plans shall be submitted to this office describing frequency and methodology of disinfection.
- 06 Used needles and sharps shall be properly treated and disposed of within 10 days of collection. All other biohazardous waste shall be incinerated or properly treated within 48 hours of collection, unless alternate plans have been specifically approved by this department.
- 07 No biohazardous waste shall be stored in Dade County without prior approval of this Department.
- 08 Transporters of biohazardous waste shall provide each customer with a receipt for all material picked up. This receipt will contain the date, type and approximate weight of biohazardous waste removed.

GENERAL CONDITIONS:

- 09 The applicant, by acceptance of this document, agrees to operate and maintain the subject operation so as to comply with the requirements and standards of Chapter 24 of the Code of Metropolitan Dade County.

File Number: 000003897

Metropolitan Dade County Department of
Environmental Resources Management


John W. Renfrow, P. E., Director

000053

Department of Environmental Protection

Lawton Chiles
Governor

Southwest District
3804 Coconut Palm Drive
Tampa, Florida 33619

Virginia B. Wetherall
Secretary

August 1, 1995

Dear Mr. Pirisky:

Re: DEP Permit No.: A053-179818

Since your biological waste incinerator on permit A053-179818 is subject to the requirements of Chapter 62-213, F.A.C. - Title V, the expiration date of that permit has been automatically extended pursuant to Rule 62-210.300(2)3.a., F.A.C. As of the date of this letter the expiration date of permit A053-179818 is January 15, 1996. Please be aware the Department is currently going through the rule making process to change the expiration date to April 1, 1996.

If you have any questions regarding this issue, please do not hesitate to call me at (813)744-6100 extension 107.

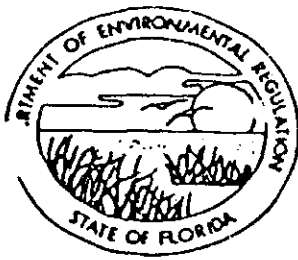
Sincerely,

"Protect, Conserve and Manage Florida's Environment and Natural Resources"

Printed on recycled paper

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Florida Department of Environmental Regulation

Southwest District

Lawton Chiles, Governor

3804 Coconut Palm

813-744-6100

Tampa, Florida 33619

Carol M. Browner, Secretary

PERMIT/CERTIFICATION:

I.D. Number: FLD 981 474 802

Permit No.: H052-195824

County: Pinellas

Issue Date: February 12, 1993

Expiration Date: February 12, 1998

Latitude / Longitude:

27°53'11"N / 82°42'19"W

Section / Township / Range:

9 / 16E / 30S

Project: Operation of Hazardous
Waste Storage Facility

This permit is issued under the provisions of Chapter 403, Florida Statutes, and Florida Administrative Code Rules 17-3, 17-25, 17-532, 17-555 and 17-730. The above named permittee is hereby authorized to operate the facility shown on the application and approved drawings, plans, and other documents, attached hereto or on file with the Department and made a part hereof and specifically described as follows:

The permittee shall be authorized to operate the hazardous waste storage facility specified in the application, on the property having a total area of 2.0 (MOL) acres located at 5303 126th Avenue North, Pinellas Park, Pinellas County, Florida.

This facility has two (2) vehicle unloading areas and four (4) waste storage areas, and associated secondary containment trenches and sumps.

The truck unloading area is a covered area 14 feet wide by 177 feet long with two containment areas each with a secondary containment capacity of 12,488 gallons each. The area is designed for two trucks with a maximum capacity of 7,000 gallons each. The container storage area is a covered building 60 feet wide by 408 feet long divided into four areas. The areas have secondary containment capacities of 4796, 1079, 1299, 9308 gallons, respectively. The four areas have storage capacities of 808, 408, 224 and 1464 containers (as 55 gallon double stacked containers).

The permittee shall be authorized to operate a transfer facility on-site in accordance with Chapter 17-730.171, F.A.C. and shall be authorized to store manifested hazardous waste on the paved lot within the facility boundary for ten days as allowed for transfer facilities.

PERMIT HISTORY

HC52-084462

H052-096037

HC52-139568

ISSUED

12/2/84

8/20/86

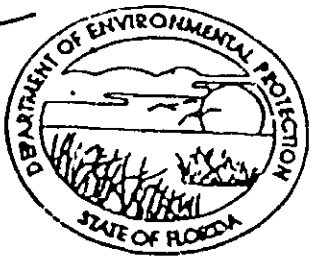
9/28/88

EXPIRED

10/31/86

8/20/91

6/30/92



Florida Department of Environmental Protection

Southwest District

Lates Chica, Governor

3804 Coconut Palm Dr.

813-744-6100

Tampa, Florida 33619

Virginia Wetherell, Secretary

PERMIT/CERTIFICATION:

I.D. Number: FLD 980 729 610

Permit No.: HO53-182726A

County: Polk

Issue Date: Dec. 10, 1991

Expiration Date: Dec. 10, 1996

Minor Modification Date: SEP - 8 1993

Latitude / Longitude:

27°57'05"N / 81°47'09"W

Section / Township / Range:

23 / 29E / 25S

Project: Operation of a
Hazardous Waste
Storage and Fuel
Blending Facility

This permit is issued under the provisions of Chapter 403.722, Florida Statutes, and Florida Administrative Code Rules 17-730. The above named permittee is hereby authorized to perform the work or operate the facility shown on the application and approved drawings, plans, and other documents, attached hereto or on file with the Department and made a part hereof and specifically described as follows:

To operate a hazardous waste storage and fuel blending facility located at 170 Bartow Municipal Airport in Bartow, Polk County, Florida.

Permitted hazardous waste storage includes storage in tanks and containers. Container storage is conducted in the southern half and a small portion of the northern half of a roofed drum storage building. Other activities in the northern portion of the building include drum staging (arranged 8 rows by 12 pallets deep) and fuel blending. The building dimensions are 125 feet 3 inches by 120 feet 3 inches. Drum storage capacity is 81,180 gallons or the volume equivalent of 1476-55 gallon drums. The southern drum storage area consists of 15 rows whereas the northern drum storage, located next to the fuel blending area, consist of 1 row. Each linear row in the southern and northern storage area may have up to 12 and 7 pallets respectively. Drums are stacked 4 to a pallet and up to 2 pallets high. Minimum aisle space at the storage area is 3 feet. All drums are stored under sprinklers.

Storage in tanks includes ten 6800 gallon tanks designated as T-101 through T-110, and two 7,000 gallon bottoms tanks designated as R-202 and R-203. Blending of hazardous waste fuels in tanks includes one 680 gallon tank designated as T-111 and two 980 gallon tanks designated as T-112 and T-114.

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J. Vincent Nabholz,¹ Richard G. Clements,¹ Maurice G. Zeeman,¹ Kimberly C. Osborn,² and Roberta Wedge²

VALIDATION OF STRUCTURE ACTIVITY RELATIONSHIPS USED BY THE USEPA'S OFFICE OF POLLUTION PREVENTION AND TOXICS FOR THE ENVIRONMENTAL HAZARD ASSESSMENT OF INDUSTRIAL CHEMICALS

1903 a

REFERENCE: Nabholz, J. V., Clements, R. G., Zeeman, M. G., Osborn, K. C., and Wedge, R., "Validation of Structure Activity Relationships Used by the USEPA's Office of Pollution Prevention and Toxics for the Environmental Hazard Assessment of Industrial Chemicals," Environmental Toxicology and Risk Assessment: 2nd Volume, ASTM STP 1173, Joseph W. Gorsuch, F. James Dwyer, Christopher G. Ingersoll, and Thomas W. La Point, Eds., American Society for Testing and Materials, Philadelphia, 1993.

ABSTRACT: The Toxic Substances Control Act (TSCA) allows for the regulation of new industrial chemicals if a chemical may present an unreasonable risk towards the environment or if a chemical has significant exposure towards the environment. As part of this regulatory process, an environmental hazard assessment is used to identify the effects of a chemical towards organisms in the environment, and their populations, communities, and ecosystems. In the United States Environmental Protection Agency's (USEPA) Office of Pollution Prevention and Toxics (OPPT), the aquatic toxicity of chemicals has been predicted using structure activity relationships (SAR) because of a lack of measured toxicity data. A SAR is the relationship between a chemical's toxicity and its chemical structure. Quantitative and qualitative SARs have been developed

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²Scientist and project manager, respectively, ICF Inc., Clement International Corp., 9300 Lee Highway, Fairfax, VA 22031-1207.

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for dozens of chemical classes and their validation has been an ongoing process in OPPF since 1981.

The object of SAR validation is to test a SAR's accuracy and consists of comparing the predicted toxicity values of chemicals with the measured toxicity values. When predicted and measured values are similar, the SAR is assumed to be accurate. When the predicted and measured values are significantly different, either the SAR is reformulated or a new SAR is identified for another chemical class. The goal of SAR validation is to increase the accuracy of SARs. Newly measured toxicity data are either integrated into existing SARs or used to develop new SARs.

A summary and discussion of this validation process for several chemical class will be presented: neutral organic chemicals, organic chemicals which show excess toxicity relative to neutral organic chemicals with similar structure, anionic surfactants, cationic surfactants, polycationic polymers, cationic dyes, acid dyes, polyanionic monomers which are strong chelators of nutrient elements, and compounds which undergo hydrolysis (e.g., acid chlorides and alkyloxysilanes).

KEYWORDS: environmental hazard assessment, structure activity relationships, validation, aquatic toxicity, acute toxicity, chronic toxicity, toxicity assessment, Toxic Substances Control Act

INTRODUCTION

The Toxic Substances Control Act (TSCA) allows for the regulation of new industrial chemicals under Sec. 5 if a chemical may present an unreasonable risk towards the environment or if a chemical has significant exposure to the environment. As part of this regulatory process, an environmental hazard (or toxicity) assessment is developed to identify as many of the effects of a chemical as possible towards organisms in the environment, including their populations, communities, and ecosystems. The standard toxicity profile for all chemicals assessed for potential risk to aquatic ecosystems consists of the following effective concentrations (EC): . . .

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fish acute toxicity (96 h LC_{50});
daphnid acute toxicity (48 h LC_{50});
green algal toxicity (96 h EC_{50});
fish chronic value (ChV);
daphnid ChV; and
algal ChV.

The chronic value (ChV) for fish and aquatic invertebrates is the same as a chronic no-effect-concentration (NEC) and the geometric mean of the maximum allowable toxicant concentration (MATC). The MATC is the range of concentrations between the lowest-observed-effect concentration (LOEC) and the no-observed-effect concentration (NOEC). The ChV for green algae is the 96 h NEC. If the 96 h NEC is not available, then the 96 h NOEC is used, and if the NOEC is not available, then the 96 h EC_{10} is used. In some cases, the algal ChV is predicted by dividing the 96 h EC_{50} by 4.0.

A toxicity profile is predicted for every chemical assessed by OPPT using its chemical structure, its physical/chemical properties, and SAR methods. The goal of OPPT is to predict all six ECs for all chemicals, however, about half the time only the environmental base set of ECs can be predicted, i.e., the fish acute value, the daphnid acute value, and the algal toxicity value. Occasionally, only one EC is available for a chemical. For a more detailed discussion of OPPT's environmental SAR methods, see Nabholz et al. (1993).

OPPT has used structure activity relationships (SAR, Auer et al. 1990; Nabholz et al. 1993; Clements 1988, 1993a, 1993b) since 1979 to predict the toxicity of 95% of new chemicals reported under Sec. 5 of TSCA. To date, over 20,621 chemicals described in Sec. 5 premanufacturing notices (PMN) have been assessed by OPPT for environmental risk. Most of these assessments have been based on toxicity predictions derived from the chemical structure and physical/chemical properties reported in the PMN. Only about 4.8 percent of these PMNs have contained test studies for environmental toxicity. Of course, if measured toxicity data are available for a chemical, then those data are used for risk assessment provided that those data are valid.

OPPT began to use structure activity relationships (SAR) in 1979 and quantitative structure activity relationships (QSAR) in 1981. Use of QSARs has become more and more frequent. A QSAR is simply a regression equation between a chemical's toxicity and one or more of its physical/chemical properties. QSARs have been developed from as little as one datum, i.e., one fish acute value, to dozens of data points for a chemical class.

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The science of SAR consists not only of (1) QSARs, but also, (2) nearest analog analysis which uses the closest structural analog or the two analogs which bracket a chemical to predict toxicity because no physical/chemical property has been found to be correlated with the toxicity for the chemical class, and (3) generic evaluations of a particular chemical class, e.g., acid dyes. For a more detailed discussion of SAR as it is used by OPPT see Auer et al. 1990; Nabholz 1991; Nabholz et al. 1993; Zeeman et al. this volume.

SAR validation within OPPT is done by measuring how accurately the toxicity of a chemical was predicted. This method of validating SARs is common and was used early in the development of environmental SARs (Konemann 1981). When OPPT requests that the chemical industry test a chemical for toxicity, OPPT determines how close the measured toxicity values are to the predicted values. One requirement is that the measured value be determined under similar test conditions as were used to test the chemicals included in the SAR. For example, OPPT predicts the toxicity of aliphatic amines from an SAR in which all the toxicity data were measured at about pH 7 or completely ionized. Therefore, when an amine is tested, OPPT requests that the stock solution be neutralized prior to testing.

Validation of all environmental toxicity SARs has been an ongoing process in OPPT since 1981. As soon as new SARs or QSARs are developed, predictions become hypotheses to be tested. Testing results are integrated into existing SARs or used to create new SARs whenever new toxicity information becomes available.

Validation in this study was conceptualized as a validation ratio, i.e., the predicted toxicity value (P-EC) divided by the measured toxicity value (M-EC). If this ratio was 1.0, perfect accuracy would be demonstrated. Ratios less than 1.0 would indicate that toxicity had been over-predicted, and ratios greater than 1.0 would indicate that toxicity had been under-predicted. Perfect accuracy is the goal of OPPT with regards to SAR analysis, but we all know that the real world is more variable than not. For example, differences in species sensitivity is generally 10 times or greater and the results of interlaboratory tests (or round robin or ring tests) frequently show differences of 10 times or more (Zeeman et al. this volume).

The pragmatic goal of OPPT's SAR program has been that predicted values be within a factor of 10 of the measured values, i.e., ratios of 0.1 to 10.0. If a validation ratio fell outside this range, then an adjustment of the SAR for the chemical class was required. For example, if a measured toxicity value indicated that a chemical was more than 10

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times more toxic than predicted by our current SAR, then the chemical was characterized as exhibiting excess toxicity (Auer et al. 1990; Lipnick 1991) and a new SAR for that subclass was usually developed. A more specific goal was to have mean validation ratios be slightly less than 1.0. If perfect accuracy could not be obtained, then OPPT should reasonably over-predict the toxicity of new chemicals because the U.S. Environmental Protection Agency is a regulatory agency whose goal is to protect the environment. Auer et al. (1990); Nabholz (1991); and Nabholz et al. (1993) have more detailed discussions of the role of SAR in OPPT's risk assessment process, and Suter (1993) discussed SAR in the broader context of ecological risk assessment.

We also realized that the mean validation ratios were more important than the range of ratios. The range of ratios from 1979 to present would represent a historical range. A historical range would contain all mistakes and would not reflect the adjustments which had been made in the SAR Program over the years. For example, toxicity predictions for a chemical assessed in Fiscal Year (FY) 1985 were made using the current SAR methods available for the chemical class in FY85. If the measured toxicity information for the chemical indicated that the toxicity was significantly over or under predicted, then the SAR was adjusted using the measured toxicity data for the chemical class so that future predictions for the chemical class would be more accurate. The original predictions were not changed, thus, the ranges observed in this validation study reflect all of the inaccuracies inherent in the SAR Program since 1979.

METHODS

Test study summary sheets were analyzed for predicted and measured toxicity values and ratios were calculated. Ratios were then sorted by chemical class and toxicity endpoint. As an ongoing activity, OPPT summarizes the results of each environmental toxicity test submitted under TSCA. For each toxicity test, a test study summary sheet is prepared which summarizes the pertinent data from the toxicity test regarding the chemical tested, species tested, testing conditions, and effective concentrations, such as, EC_{50} , LC_{50} , LC_{100} , EC_{100} , LOEC, NOEC, NEC, EC_{90} , and EC_{10} . The toxicity summary sheets are contained in a database called the OPPT PMN ECOTOX DATABASE and the physical/chemical information is contained in the OPPT PMN PHYCHEM DATABASE.

A contractor

was hired to analyze these summary sheets. The following guidelines were used during this evaluation: (1) only aquatic toxicity studies which contained data identical to the six ECs which comprise OPPT's standard toxicity

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profile were to be used, however, if a daphnid 24-h LC_{50} value, a fish 72-h LC_{50} value, and a green algal 72-h EC_{50} value were the only ECs available, then they were used, (2) studies were limited to those which has been validated by Nabholz in order to ensure consistency in data evaluation, (3) the only toxicity predictions used were those made with OPPT environmental SAR methods and by Nabholz, again for consistency, (4) toxicity values were not used if they were significantly higher than either the aqueous solubility limit of non-surfactant chemicals or the dispersibility limit of self-dispersing surfactants and polymers, (5) studies in which the chemical identity of the tested substance was not sufficiently known to allow for predictions were not used, (6) studies not used included those in which the new chemical was tested as a minor component, e.g., 5 percent active ingredients (AI), and was tested with other components which were known to be toxic to aquatic organisms, and (7) studies done in dilution water which was known to contain material which would interfere significantly with the intrinsic toxicity of the chemical were also rejected. For example, OPPT predicts the toxicity of polycationic polymers assuming dilution water will contain less than 2.0 mg/L (ppm) of total organic carbon (TOC). Therefore, when a polycationic polymer was tested in dilution water containing 12.0 mg TOC/L, the study was not used.

Since 1989, OPPT has been routinely predicting the toxicity of every chemical submitted under Sec. 5 even when measured toxicity values were included in the PMN. We realized that this was the best way to improve the SAR analysis. Prior to 1989, predictions were not routinely done when measured toxicity values accompanied a PMN. Therefore, when the contractor found measured toxicity values but no predicted values during searches of the PMN ECOTOX DATABASE, a list of the PMNs with no or a partial set of predicted toxicity values was sent to Nabholz. Nabholz predicted the toxicity of these chemicals based solely on the chemical's physical/chemical properties and SAR methods used at the time of submission, and returned the predictions to the contractor for inclusion in the study.

During the actual calculation of validation ratios, two problems arose which needed resolution. (1) When the predicted toxicity value was "greater than 100 mg/L" which indicated a low toxicity concern by OPPT, and the measured value was greater than 100 mg/L, then the "greater than" symbol was dropped and a ratio calculated using 100. This situation occurred with several chemical classes (Nabholz et al. 1993) which generally have low toxicity to fish and daphnids, have no QSAR, and whose SARs are characterized as generic evaluations or statements about their aquatic toxicity. For example, such classes include acid dyes with three or more sulfonic acid groups, amphoteric dyes, small

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molecular weight acids at pH 7.0 and which are not surfactants, polyanionic monomers, polyanionic polymers, nonionic polymers, and small molecular weight quaternary nitrogens at pH 7.0 and which are not surfactants. Likewise, when the predicted value was "greater than 100 mg/L" and the measured value was less than 100 mg/L, the "greater than" symbol was ignored and the ratio calculated.

(2) When the predicted value was "no effects at saturation" and a valid toxicity value was measured or when a toxicity value was predicted and the measured value was "no effects at saturation," no ratio was calculated because the numeric value that should be assigned to "no effects at saturation" was not known. This situation occurred most frequently with predictions of chronic toxicity. Many QSARs for chronic toxicity proceed from predictable ChVs to "no effects at saturation" as K_{ow} increases. Therefore, concentrations of a chemical which cause chronic effects and concentrations which are not toxic at saturation for the exposure period of the test may be very close together, e.g., 10.0 $\mu\text{g/L}$ (ppb) and 5.0 $\mu\text{g/L}$.

Sample Size

Test data from 462 chemicals were included in the validation analysis. There were seven sources of information: (1) TSCA Sec. 5 PMNs, (2) TSCA Sec. 5 Low Volume Exemptions (LVE) which are new chemicals whose production volume will be less than 1000 kg/year, (3) TSCA Sec. 5 Test Market Exemptions (TME) which are new chemicals will be test marketed before commercial production, (4) TSCA Sec. 8(e) submissions which are chemicals which may present a substantial risk of injury to the environment, (5) TSCA Sec. 8(e) submissions which are toxicity data for the Agency's information only, i.e., For Your Information (FYI), (6) TSCA Sec. 5 Pre-Notice Communications (PC) which are information packages submitted prior to submission of a PMN, and (7) toxicity information from the Organization for Economic Co-operation and Development (OECD) high production volume (HPV) screening information data set (SIDS) program. The distribution of chemicals by source and year is:

1	PMN (FY 1981);
1	PMN (FY 1982);
6	PMN (FY 1983);
4	PMN (FY 1984);
8	PMN (FY 1985);
7	PMN (FY 1986);
45	PMN (FY 1987);
88	PMN (FY 1988);
1	LVE (FY 1988);
51	PMN (FY 1989);
3	LVE (FY 1989);
3	TME (FY 1989);

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50 PMN (FY 1990);
 2 LVE (FY 1990);
 1 TME (FY 1990);
 84 PMN (FY 1991);
 3 LVE (FY 1991);
 38 PMN (FY 1992);
 14 Sec. 8(e);
 2 Sec. 8(e) FYI;
 1 Sec. 5 PC;
 1 SIDS; and
 48 Toxicity data for analogous chemicals or positive control chemicals submitted with PMNs.

The distribution of chemicals by chemical class is listed below. Descriptions of these chemical classes have been discussed by Nabholz et al. (1993).

70 Neutral organic/solvent-like chemicals;
 124 Organic monomers with excess toxicity;
 8 Acids;
 19 Polyanionic monomers;
 75 Dyes:
 20 Cationic dyes,
 50 Acid (anionic) dyes,
 3 Neutral (nonionic) dyes, and
 2 Amphoteric dyes;
 77 Surfactants:
 9 Cationic,
 42 Anionic,
 25 Nonionic, and
 1 Amphoteric;
 79 Polymers:
 35 Cationic,
 37 Anionic,
 4 Nonionic, and
 3 Amphoteric; and
 10 Metals.

RESULTS

Distribution of Validation Ratios

Ratios for 920 effective concentrations (EC) were calculated and their distribution by type of effective concentration was:

414 Fish 96-h LC_{50} ;
 307 Daphnid 48-h LC_{50} ;
 145 Green algal 96-h EC_{50} ;
 8 Fish ChV;
 14 Daphnid ChV; and
 32 Algal ChV.

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The frequency distribution of ratios was plotted on an arithmetic scale (Fig. 1). As expected, this histogram showed that the distribution was strongly skewed to the larger ratios; therefore, the ratios were plotted on a logarithmic scale (Fig. 2). The skewed distribution was expected because all ratios of less than 1.0 would be summarized in the ratio class of 0.0 to 1.0. This transformation approached a normal distribution. The ratio class with the highest frequency was 0.95 to 0.05 or 1.0. Eighty-five percent (782/920) of the ratios were ≥ 0.1 and ≤ 10.0 . Only 9 percent (83/920) of the ratios were < 0.1 and only 6 percent (55/920) were > 10.0 .

Mean Validation Ratios

The geometric mean ratio was calculated for each EC in the OPPT standard toxicity profile:

0.64	Fish 96-h LC ₅₀ ;
0.79	Daphnid 48-h LC ₅₀ ;
0.81	Green algal 96-h EC ₅₀ ;
0.24	Fish ChV;
0.39	Daphnid ChV; and
1.07	Algal ChV.

The most accurately predicted effect was the algal ChV and the most inaccurately predicted effect was fish ChV. The fish ChV was also the endpoint with the smallest sample size, having only 8 ratios. The grand mean based on all 920 ratios was 0.72. On the average and with one exception, toxicity was over-predicted, although only 4 times.

The mean ratios for each toxicity endpoint for 60 chemical classes are listed in Table 1. As was expected, ratios were much more variable with a range from 0.01 to 410.0.

DISCUSSION

The results of this validation study were both surprising and expected. We were surprised because the results came out better than anticipated. We expected the results to support our SAR methods, because for years we knew we were doing well predicting toxicity. We frequently received positive feedback from the chemical industry about how well we had predicted the toxicity of their chemical(s), but this feedback was only on a case-by-case or chemical-by-chemical basis. It was easy to remember the accurate predictions, but much harder to figure out why some chemicals were significantly under or over predicted.

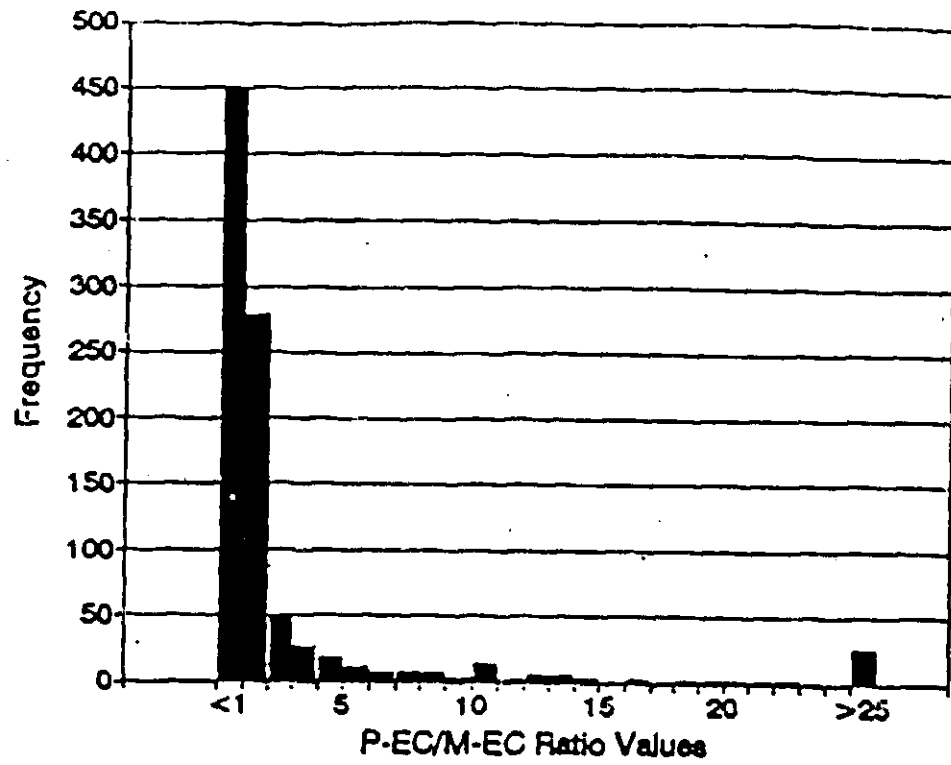


FIG. 1--Histogram of validation ratios on an arithmetic scale.

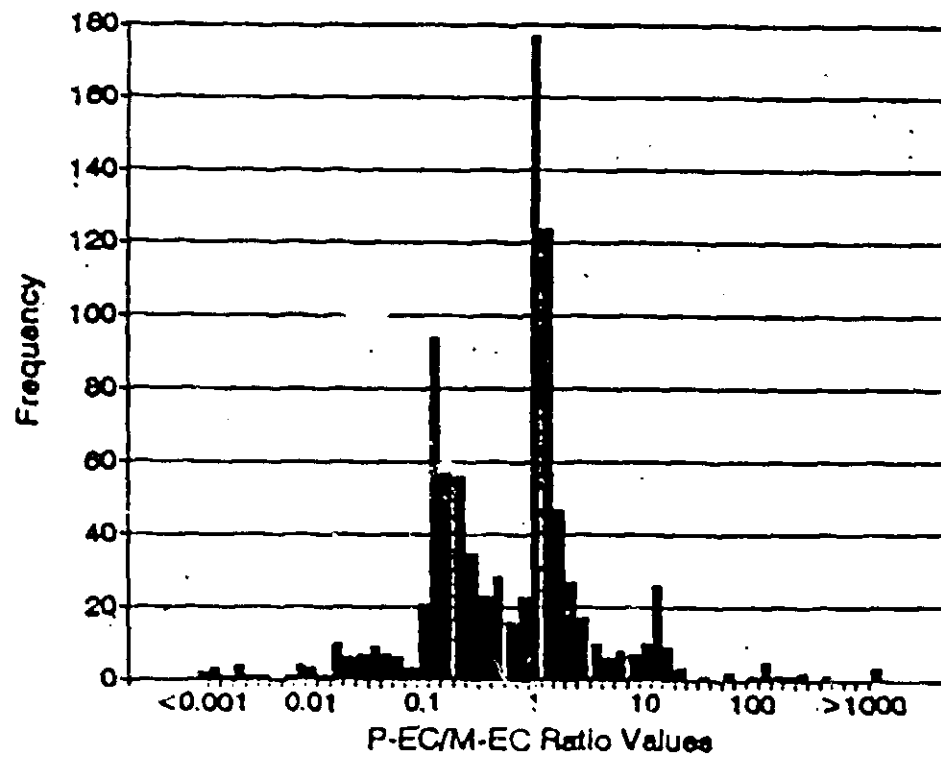


FIG. 2--Histogram of validation ratios on a logarithmic scale.

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TABLE 1--Validation ratios by chemical class. Ratios are geometric means. Dashes indicate that no ratio was available. For classes which are subdivided, e.g., acid dyes, the class ratio is reported along with ratios for each subclass. S# indicates the number of sulfonic acids on the dye.

CLASSES	P-EC/M-EC RATIOS					
	Fish 96h LC50	Daphnid 48h LC50	Green Algae 96h EC50	Fish ChV	Daphnid ChV	Green Algae ChV
Acid Chlorides	0.7	1.0	-	-	-	-
Acids	0.8	0.9	2.0	-	-	-
Acrylamides	0.2	0.2	-	-	-	-
Acrylates	0.7	0.3	2.9	-	-	10.0
Aldehydes	-	1.0	-	-	-	-
Alkylsilanes	3.1	0.1	0.6	-	-	-
Allyl Ethers	1.4	-	-	-	-	-
Allyl Ketones	2.4	-	-	-	-	-
Aliphatic Amines	0.9	0.5	2.7	-	-	0.3
Anilines	1.2	0.6	-	-	-	-
Benzothiazoles	2.0	-	1.4	-	-	-
Benzotriazoles	0.8	0.3	2.3	-	-	-
Carbamates	2.0	1.0	0.2	-	-	1.1
Chlorosilanes	0.2	0.1	-	-	-	-
Diazos	1.0	-	-	-	-	-
Dinitrobenzenes	0.1	0.2	20.0	-	-	15.0
Dithiocarbamates	1.0	1.0	-	-	-	-
Dipoxides	0.1	-	-	-	-	-
<u>Dyes</u>						
Acid Dyes	0.3	0.3	0.4	-	0.1	0.01
S1,S2	0.4	0.3	0.4	-	0.1	-
≥S3	0.2	0.3	0.3	-	-	0.01
Cationic Dyes	0.9	0.8	3.0	2.3	-	-
Amphoteric Dyes	0.8	0.1	-	-	-	-
Neutral Dyes	1.0	1.0	-	-	-	-
Esters	1.0	1.0	1.6	-	-	-
Halo Alkyls	3.2	111.0	-	-	-	-
Halo Amides	1.1	0.5	-	-	0.4	-
Hydrazines	-	0.1	-	-	-	-
Isoocyanates	410.0	0.01	0.01	-	-	-
Melamines	0.4	0.8	1.0	1.0	1.0	1.0

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TABLE 1--Continued.

CLASSES	P-EC/M-EC RATIOS					
	Fish 96h LC50	Daphnid 48h LC50	Green Algae 96h EC50	Fish ChV	Daphnid ChV	Green Algae ChV
<u>Metals</u>						
Iron	0.1	0.8	-	-	-	-
Silver	-	2.0	-	-	-	-
Tin	1.3	0.7	-	-	-	-
Titanium	0.1	-	-	-	-	-
Vanadium	0.9	-	-	-	-	-
Zinc	0.2	1.5	5.4	-	-	7.7
Zirconium	0.1	-	-	-	-	-
<u>Methacrylates</u>	0.7	1.4	-	-	-	-
<u>Monomers</u>						
Polyamphoteric	23.0	1.2	0.3	-	-	-
Polyanionic	0.2	0.3	0.7	0.3	0.4	11.0
<u>Neutral Organics</u>	1.2	1.1	1.2	0.2	0.3	3.1
<u>Peroxy Acids</u>	80.0	14.0	-	-	-	-
<u>Phenols</u>	1.6	1.1	2.1	0.1	0.4	0.4
<u>Phosphates</u>	7.1	19.0	0.4	-	-	-
<u>Phosphites</u>	1.0	-	-	-	-	-
<u>Polymers</u>						
Polyamphoteric	0.2	0.1	0.03	-	-	0.4
Polyanionic	0.3	0.4	0.2	0.3	1.6	0.1
Polycationic	0.2	2.5	0.5	-	-	3.3
C backbone	0.2	1.0	0.4	-	-	3.3
Si backbone	0.2	24.0	19.0	-	-	-
Polynonionic	0.7	1.0	-	-	-	-
<u>Salicylates</u>	0.2	2.9	2.5	-	-	-
<u>Sulfonamides</u>	13.0	4.1	13.0	-	-	-
<u>Sulfonates</u>	-	0.3	0.05	-	-	-
<u>Surfactants</u>						
Amphoteric	58.0	5.4	1.4	-	-	-
Anionic	0.6	1.1	0.9	-	-	3.3
Cationic	0.9	5.3	10.0	-	-	-
Nonionic	0.9	1.0	1.1	2.5	0.2	0.6
<u>Thiols</u>	-	1.0	-	-	-	-
<u>Triazines</u>	27.0	14.0	2.2	-	-	-

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The great majority of ratios were within 10 times of perfection, i.e., ≥ 0.1 to ≤ 10.0 , and the grand mean was 0.72. The grand mean was close to 1.0 and it was slightly less than 1.0 which, as a regulatory program, is where it should be if it can not be 1.0. The mean ratios for the toxicity endpoints indicated that we predicted the environmental base set of toxicity values, i.e., the fish acute value, the daphnid acute value, and the algal toxicity value, with more accuracy than the chronic values for fish and daphnids. Given hind-sight, this is exactly the result we should have anticipated because this analysis reveals that we had 33 times more information about acute toxicity to fish and daphnids than about chronic toxicity. OPPT has much more experience with acute toxicity than with chronic toxicity, and Clements et al. (1993b) shows that OPPT has many more acute toxicity QSARs for fish and daphnids than chronic toxicity QSARs.

Only 6 percent of the chemicals were significantly under predicted and only 9 percent of chemicals were over predicted. These percentages were smaller than expected. Some of the reasons for under predicting toxicity include: excess toxicity, missing fragment constants used to predict the octanol/water partition coefficients (K_{ow}), lack of knowledge about the exact chemical structure, and no physical/chemical properties available to relate to toxicity. Some of the reasons for over predicting include: no QSAR for a class of chemicals, comparing predicted "greater than" toxicity values with actual measured values, comparing fish 96 h LC_{50} values with 72 h LC_{50} values, comparing daphnid 48 h LC_{50} values with 24 h LC_{50} values, comparing green algal 96 h EC_{50} values with 72 h EC_{50} values, predicting toxicity for chemicals with molecular weights greater than 600 or with large cross-sectional diameters, and predicting toxicity for neutral organic chemicals which are solids at room temperature.

Excess Toxicity

Chemicals with excess toxicity (Auer et al. 1990; Lipnick 1991; Nabholz et al. 1993) has probably been the largest cause of under estimating toxicity since 1979. Chemicals are assumed to have only baseline toxicity (or narcosis) until measured toxicity data show significant excess toxicity, i.e., a measured toxicity value at least 10 times more toxic than predicted by the SARs for neutral organic chemicals (Auer et al. 1990, Nabholz et al. 1993). If a chemical has a chemical structure which suggests a high probability of excess toxicity, e.g., a chemical which could belong to a class of chemicals used as pesticides (Lipnick 1991), OPPT may divide the toxicity prediction by an excess toxicity factor, say 10, but more likely a "less than" symbol is used with the toxicity prediction and a larger assessment factor (Nabholz 1991; Nabholz et al. 1993; Zeeman

et al. this volume) is used during risk assessment. Once measured toxicity data are obtained for a chemical suspected of having excess toxicity, the excess toxicity is quantified and, if large enough, a new SAR is developed for that class of chemical.

Some chemicals are never suspected of having excess toxicity, yet when measured toxicity data are obtained, are showed to have excess toxicity. For example, schiff bases were considered no more toxic than aliphatic amines, however, when the first fish acute toxicity study was obtained for a schiff base, it had a significant amount of excess toxicity. Therefore, OPPT developed a SAR for schiff bases and classified them as a subclass of aliphatic amines.

Some reactive chemicals were assumed to be of little concern because they were predicted to be transformed quickly to less toxic chemical(s). For example, aromatic diazoniums were assumed to react so quickly to form a phenol that aquatic organisms were not expected to be exposed to the diazonium, only the resulting phenol. However, when OPPT received its first toxicity data for diazoniums through TSCA Sec. 8(e), diazoniums were shown to be significantly more toxic than the resulting phenol.

Missing Fragment Constants

OPPT uses calculated K_{ow} and molecular weight (MW) in most of its QSARs. The computer program, CLOGP Ver. 3.3, is used to calculate K_{ow} . The computer program, CLOGP, calculates the K_{ow} of organic chemicals using chemical structure and fragment constants for each portion of the chemical structure (Hansch and Leo 1979). When a missing fragment does not permit CLOGP to complete the calculation, OPPT staff must estimate a value for the missing fragment or find some test data for an analog. If the K_{ow} is inaccurate for a chemical, then the resulting toxicity prediction will also be inaccurate.

Exact Chemical Structure

Lack of sufficient knowledge about the chemical structure, especially, for reaction products and dyes, can lead to significant underestimations of toxicity. A toxicity prediction is only as good as the knowledge of a chemical's structure. If you change the structure, you must repredict toxicity. Many reaction products and some dyes are only known by their representative structure. For example, the range of fish acute (96 h LC_{50}) toxicity values for 27 cationic dyes with delocalized cationic charge varies 1,200 times. Many of these dyes are described by their representative structure only, tested products may contain several chemical structures and numerous impurities, and there is no physical/chemical property identified which

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is strongly correlated to toxicity. OPPT uses the nearest analog SAR method to predict toxicity for these types of chemicals.

Chemical Reactivity

OPPT must attempt to estimate chemical reactivity from structure alone. OPPT has neither super computers that can be easily accessed to estimate exotic molecular descriptors of chemical reactivity nor widely-accepted laboratory tests that can be used to measure reactivity. OPPT has to use simple physical/chemical properties, such as K_{ow} , MW, number of reactive groups per molecule, e.g., epoxides, charge density of cationic polymer, number of aliphatic carbons in the hydrophobic component of a surfactant, or number of ethoxy groups in a nonionic surfactant, in its SARs. For example, if monoepoxides and diepoxides are used in the same SAR without accounting for the extra reactivity due to the second epoxide, predictability using K_{ow} and MW alone is poor. However, if an SAR is developed using only monoepoxides and another SAR is developed using diepoxides, excellent predictability can be achieved using only K_{ow} and MW. This approach requires that OPPT have more SARs for a chemical class and will make OPPT more dependent on measured toxicity information, but, as this validation study has shown, excellent predictability can be obtained using simple methods.

Classes lacking a QSAR

Some chemical classes lack a QSAR (Auer et al. 1990; Nabholz et al. 1993) and the nearest analog method may also be a poor method for predicting toxicity. Some of the chemical classes falling into this category are polyanionic monomers, polyanionic polymers, acid dyes, and metal-complexes with organic acids and/or aliphatic amines. Polyanionic monomers and polyanionic polymers are toxic only to green algae because of over chelation of nutrient elements; acid dyes with more than three sulfonic acids per molecule are toxic only to algae through shading of visible light; acid dyes with only one or two sulfonic acids may be toxic to fish and daphnids as well as shading algae from growing; and metal-organic acid/chemical complexes may be toxic to one or all groups of aquatic organisms depending on the stability of the complex and/or the metal's bioavailability. Toxicity is difficult to predict for all of these groups because OPPT does not have a physical/chemical property that can be easily derived from the chemical's structure and used to predict toxicity. For example, polyanionic monomers chelate nutrient elements, such as calcium, magnesium, and iron, to such an extent that green algae are inhibited from growing in the algal bottle assay. The chelation ability of polyanionic monomers depends on the number of acids per molecule, the type of

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acid (e.g, carboxylic or phosphoric), the arrangement of the acids on the molecule, the presence of nitrogen in the molecule, and the type of salt. It is very difficult to accurately predict the algal 96 h EC₅₀ value just by comparing structures. Therefore, when a close match between a chemical with known toxicity and a new chemical cannot be made, OPPT generally assumes that the new chemical will be just as toxic as the average polyanionic monomer which is about 3.0 mg/L as an algal 96 h EC₅₀. If the new chemical is tested and shows no inhibition of algal growth at 1000.0 mg/L, then the toxicity has been over-predicted by over 300 times. However, the database has been increased with one more analogous chemical for future use. ✓

Molecular Weights Greater Than 600

OPPT predicts the toxicity of neutral organic chemicals with molecular weights up to 1000 daltons even though it has been reported that uptake decreases exponentially with MWs >600 (Zitko 1981). SAR analysis has shown that toxicity decreases as MW increases at a given K_{ow} value (Clements 1988, 1993b) and OPPT has only a few test data in its PMN ECOTOX DATABASE which show significant decreases in toxicity when MWs are greater than 600. Toxicity data for organic chemical monomers with MWs >600 and <1000 are rare. Predicting the effect of MW on toxicity when most of the chemicals in a SAR have MW <300 is difficult. OPPT knows that toxicity will decrease but the extent of the decrease is not known.

Cross-Sectional Diameter

The effect on toxicity of increasing the minimum cross-sectional diameter of a neutral organic chemical above the cross-sectional diameter of hexabromobenzene is analogous to the discussion on increasing MW. Minimum cross-sectional diameter is difficult to predict without the use of a mainframe computer. While it is known that increasing cross-sectional diameter will decrease toxicity, this property is rarely taken into account when doing predictions because the relationship between the cross-sectional diameter and toxicity cannot yet be determined with adequate accuracy and, if errors are made, they have to be on the side of safety.

Solids

Most of the organic chemicals used in OPPT SARs are liquids at room temperature. As the melting point (MP) of a chemical increases, the water solubility (WS) is known to decrease (Banerjee et al. 1980). When OPPT predicts the toxicity of solids, it also predicts the WS if no measured ws is available and if the MP is known. The WS limit is compared to the predicted toxicity value. If the WS limit

is higher than the EC, then the prediction is considered accurate. However, if the WS limit is lower than the EC, then the certainty about the ability of the organic chemical to cause a toxic effect within the exposure period associated with the EC decreases. As a general rule, if the EC is 10 times higher the WS limit for a chemical, then OPPT predicts "no effects at saturation". However, if the EC is within 10 times of the WS of the chemical, then a toxicity prediction is made because of the uncertainty associated with predicting and measuring the WS limit of organic chemicals. For example, OPPT recently assessed a series of dinitrobenzenes for acute and chronic toxicity. All were solids at room temperature and only some MPs were known. Predictions of toxicity and WSs suggested that most of the dinitrobenzenes would be toxic in acute toxicity tests. Therefore, acute toxicity testing was recommended. When the test results were reviewed, it was apparent that the WS estimates were higher than measured values and most of the acute toxicity testing resulted in no effects at saturation. These new data permitted the reformulation of the SARs for dinitrobenzenes with respect to the environmental base set of tests.

CONCLUSIONS

In spite of the uncertainties inherent in predicting and measuring the toxicity of industrial chemicals, this study reveals that OPPT does an acceptable job in developing and using SAR Analysis for most classes of chemicals. OPPT will continue to validate its environmental SARs and continue to strive toward perfection in its SAR toxicity predictions. Although OPPT appears to be doing an adequate job in predicting environmental toxicity, measured toxicity data for chemicals are always preferred than predicted toxicity data in assessments as long as the measured data are valid and appropriate for the assessment.

Accurate SAR methods are dependent on accurate toxicity testing. OPPT's major source of toxicity data is the chemical industry and commercial testing laboratories and these data are used to develop new SARs and validate existing SARs. It is important that the test data submitted accurately reflect the toxicity of a chemical under a defined set of testing conditions. OPPT's entire SAR program is dependent on accurate and valid environmental test data. This study indicates that in order to improve and extend SAR analysis to all chemical classes, there is a need for standard testing methods and greater knowledge about the physical/chemical properties of chemicals prior to testing. Chemical structure needs to be clearly defined. The nature of the chemical substance to be tested has to be also be known with as much certainty as possible, especially, with respect to reaction products that have no

definite chemical structure. The WS limit of chemicals with low WS should be measured and the dispersibility limit of surfactants should also be determined. The highest treatment concentration of toxicity tests should not exceed these WS/dispersibility limits. The amount of background dissolved organic carbon (DOC) in dilution water has to be measured when testing cationic chemicals. The reactivity of reactive organic chemicals should be determined with greater accuracy before toxicity testing. The hardness of dilution water should always be known and controlled because the average hardness of surface waters in the United States is about 120.0 mg/L as CaCO₃, and this fact should be kept in mind when testing chemicals for use/release in the U.S. For this reason, OPPT recommends that toxicity tests with fish and daphnids be done at a hardness of less than 180.0 mg/L. The pH should be known and controlled depending on the purpose of the toxicity testing. For example, if an acid is being tested for normal industrial/commercial use and release to the environment through the sewer, then it should be tested near neutral pH. If, however, the toxicity testing is to determine the environmental concern from an accidental spill, then the acid should be tested without pH adjustment.

RECOMMENDATIONS

Our advice to testing laboratories: Know what you are testing! Know why the sponsor is testing the chemical, e.g., normal use or the impact of a transportation spill. Recommend testing which corresponds to the physical/chemical properties of the chemical and control those factors, e.g., DOC when testing cationic chemicals, which you know will have the greatest influence on the toxicity of the chemical. Do not test an industrial chemical above its WS limit unless there is a specific purpose for the testing.

Our advice to the chemical industry: Tell your testing laboratory about your chemical! The more they know about your chemical, the more they can help you to test it properly. Testing laboratories have a lot of experience in testing many different types of chemicals. Remember that not much experience is gained by a testing laboratory by blindly testing unknown materials.

DISCLAIMER

This document has been reviewed by OPPT, USEPA and approved for presentation. Approval does not signify that the contents necessarily reflect the views and policies of the Agency nor does mention of tradenames or commercial products constitute endorsement or recommendation for use.

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Mode of Action and the Assessment of Chemical Hazards in the Presence of Limited Data: Use of Structure-Activity Relationships (SAR) under TSCA, Section 5

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Section 5 of the Toxic Substances Control Act (TSCA) requires that manufacturers and importers of new chemicals must submit a Premanufacture Notification (PMN) to the U.S. Environmental Protection Agency 90 days before they intend to commence manufacture or import. Certain information such as chemical identity, uses, etc., must be included in the notification. The submission of test data on the new substance, however, is not required, although any available health and environmental information must be provided. Nonetheless, over half of all PMNs submitted to the agency do not contain any test data; because PMN chemicals are new, no test data is generally available in the scientific literature. Given this situation, EPA has had to develop techniques for hazard assessment that can be used in the presence of limited test data. EPA's approach has been termed "structure-activity relationships" (SAR) and involves three major components: the first is critical evaluation and interpretation of available toxicity data on the chemical; the second component involves evaluation of test data available on analogous substances and/or potential metabolites; and the third component involves the use of mathematical expressions for biological activity known as "quantitative structure-activity relationships" (QSARs). At present, the use of QSARs is limited to estimating physical chemical properties, environmental toxicity, and bioconcentration factors. An important overarching element in EPA's approach is the experience and judgment of scientific assessors in interpreting and integrating the available data and information. Examples are provided that illustrate EPA's approach to hazard assessment for PMN chemicals.

Background

A situation that commonly confronts the U.S. Environmental Protection Agency (EPA) involves evaluating the hazard potential of chemicals in the presence of little or no test data. This situation is encountered with many industrial chemicals as well as many of the substances identified in industrial effluents, hazardous waste sites, and in environmental monitoring surveys. A 1984 report by the National Research Council (1) explored the question of the availability of toxicity test data on industrial chemicals and concluded that such chemicals often have been subjected to a minimum of testing and, not infrequently, to no testing at all. Despite the limited available test data, there is a continuing demand on EPA to provide an evaluation of the

potential hazards posed by these substances. EPA's approach to assessing chemical hazards in the presence of limited data will be discussed in this paper.

One of the areas that can serve to illustrate this discussion involves EPA's responsibility for the risk assessment of so-called new chemicals submitted to the agency under Section 5 of the Toxic Substances Control Act (TSCA) (2). New chemicals are those substances that do not appear on an inventory of existing TSCA chemicals; accordingly, notifications on these substances must be submitted for review by the EPA prior to commercial manufacture or importation. Pesticides, drugs, food additives, and certain other chemicals are controlled by other statutes and are not subject to TSCA. During the period from 1979 to 1988, over 12,000 Premanufacture Notifications, or PMNs, were submitted by the chemical industry to the agency for review (Fig. 1). Under the requirements of TSCA, Section 5, information such as chemical identity, uses, production volume, and exposure must be provided in the notification. The submission of test data, however is not required,

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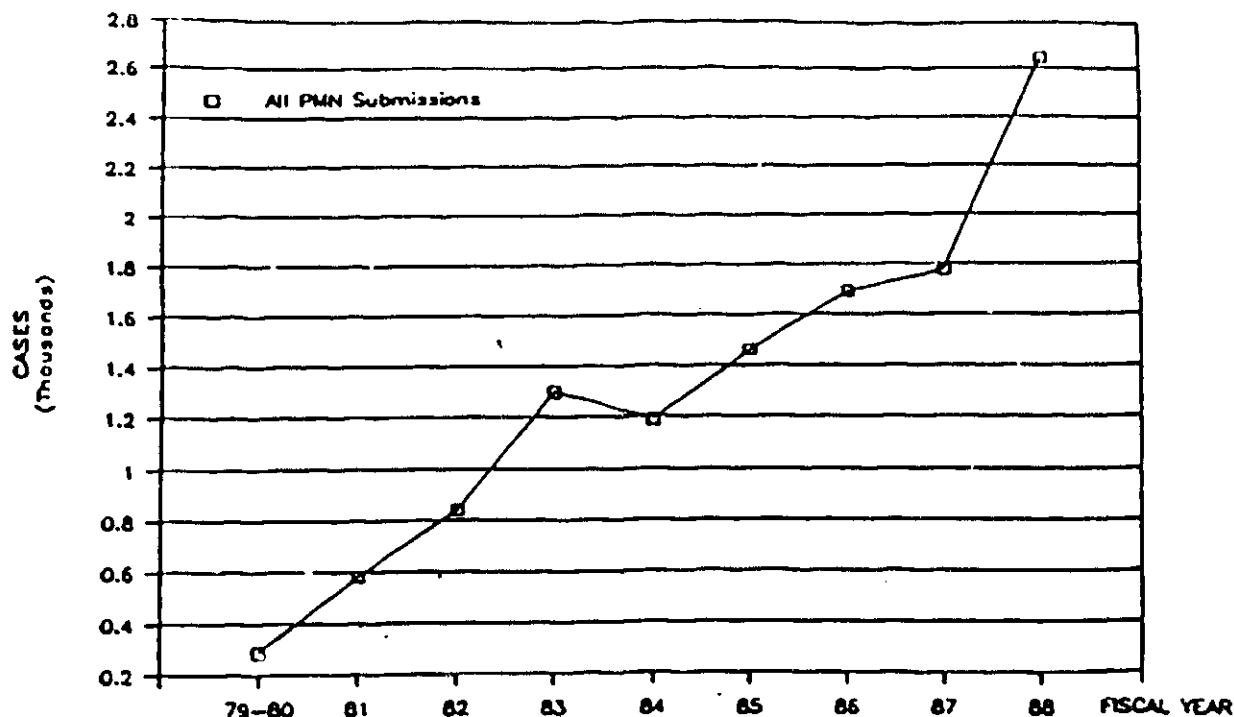


FIGURE 1. Annual receipt of PMNs (51). Fiscal year corresponds to the 1-year period starting October 1 and ending on September 30 of the following year.

Although the submitter must provide any health or environmental effects information that is available at the time of submission. Since testing for health or environmental effects is not a requirement, slightly over half of all PMN chemicals submitted to the Agency do not include any test data; because these are new chemicals no data are generally available in the scientific literature. When test data are provided (Table 1), they most commonly consist of acute toxicity and skin and eye irritation studies in laboratory animals. Data generated from other types of testing such as mutagenicity, chronic animal toxicity, ecological toxicity, and environmental fate are seen in fewer than 15% of all PMN submissions (3).

The task before EPA under TSCA, Section 5 is to reach a judgment—despite the limited test data—as to whether or not the PMN chemical under its projected conditions of manufacturing, processing, use, and disposal may or will present an unreasonable risk of injury to human health or the environment. The term risk, as used in TSCA, is some function of hazard (i.e., toxicity) and exposure, and also includes consideration of economics. When EPA has concern for the potential risks of new chemicals, or in cases where the agency is uncertain of the potential toxicity but believes that production and exposure will be significant, it can take action to control potential risks pending the development of the test data needed to adequately assess the hazards of the chemical. EPA's regulatory actions under TSCA, Section 5 generally take the form of some control or limitation on the commercialization of the new chemical pending development of test data.

As was shown by NRC (1), the limited availability of

Table 1. Test data submitted with premanufacture notices.

Type of test data	Percent of PMN*		
	All	Nonpolymer	Polymer
No test data of any type	51	38	68
Health data			
Acute toxicity			
Oral	38	50	22
Dermal	23	29	14
Inhalation	11	14	7
Local toxicity			
Eye irritation	36	47	21
Dermal irritation	38	50	22
Sensitization	11	17	5
Mutagenicity	15	23	6
Other ^b	11	16	4
Ecotoxicological data			
Acute lethal vertebrate	6	9	3
Acute lethal invertebrate	3	3	2
Environmental fate data			
Biodegradation	6	8	2
Log P	4	5	1

* Based on the PMNs received through September 1985 from data printouts retrieved from PENTA, an EPA in-house PMN information system.

^b The other health data category includes acute toxicity studies by other routes (IP, IV, etc.), repeated-dose toxicity studies (generally 28 days or less in duration), developmental toxicity, phototoxicity, neurotoxicity, and a variety of other toxicity studies.

test data on new chemicals is not unique; it is a characteristic shared by many of the chemicals for which EPA has regulatory responsibilities. For example, only limited data are available on many of the over 700 chemicals found on the Superfund list of hazardous sub-

stances (4); despite this limitation EPA is called on to evaluate the hazards and risks of these chemicals at Superfund sites.

General Discussion of Approach

The approach that EPA's Office of Toxic Substances (EPA/OTS) has developed for assessing the hazards of chemicals in the presence of limited test data has been termed structure-activity relationships (SAR) and involves the following three major components: a) critical evaluation of available data, if any, on the chemical; b) identification and selection of potential analogues and/or chemicals predicted to be key metabolites, followed by an evaluation of the test data available on these compounds; and c) use of quantitative structure-activity relationships (QSARs).

As previously discussed, few data are generally available for most PMN chemicals, thus the incorporation of inputs and understanding from the latter two components is critical in assessing the hazards of new chemicals. These components are detailed later. Implementation of analogue analysis and QSAR techniques in assessing the hazards of PMN chemicals requires the experience and judgment of scientific assessors in interpreting and integrating the data and information from these components. This is critical in assessing the relevance and use of analogues as indicators of the potential hazards of PMN chemicals and in selecting the proper QSARs and evaluating the associated predictions. The importance of expert judgment in implementing this approach cannot be minimized, and its role is clearly defined in the following discussions.

Identification and Evaluation of Analogues and Potential Metabolites

This component represents one of the unique aspects of EPA's approach. [A more detailed discussion of this component can be found in Auer and Gould (3).] In order for an analogue to be useful to EPA, it must resemble the chemical of interest in one or more critical aspects (i.e., structurally, substructurally, physicochemically, etc.) and have pertinent toxicologic or other data available in the literature. A major constraint on the usefulness of any potential analogues, however, is the generally limited availability of test data on TSCA existing chemicals (1).

Analogues can be suggested by EPA staff or be retrieved from several publicly available automated chemical substructure and nomenclature search systems (e.g., Structure and Nomenclature Search System (CIS, Inc., Baltimore, MD) or CAS-Online (Chemical Abstract Service, Columbus, OH)). Analogues recommended by technical staff also often provide very useful inputs to the assessment effort. These individuals also provide expert guidance in constructing the strategy for the automated analogue searches. The guidance consists of the identification, based on consideration of chemistry, metabolism, possible mechanisms of toxic-

ity, etc., of key structural features in the chemical that may be associated with toxic action or be subject to activation or deactivation. Potential analogues resembling the chemical in the structure or function of these key features are then identified using automated substructure searching techniques. [A functionally similar chemical is one which, despite substructural differences, can be considered a functional equivalent of the chemical of interest. Examples of functional equivalents could include an aromatic amine substituent in lieu of an aromatic nitro or C-nitroso group, based on the expectation of biotransformation (5); or an α , β -unsaturated ketone in lieu of an α , β -unsaturated ester, based on similar mechanistic possibilities (6).] Once a set of potential analogues has been identified, a variety of factors (for example, physical chemical properties, possible steric effects, molecular topology, etc.) become important considerations in selecting the analogues that will be subjected to a literature search for toxicological data. Only analogues that yield relevant information are used in the assessment process.

The second major aspect of this component to identify related chemicals that may be useful in the assessment involves identifying possible biotransformation products of the target chemical. Metabolism studies are rarely available on industrial chemicals and, thus, the effort focuses on assessing the metabolic potential of the chemical with the objective of identifying likely activation and deactivation pathways. In assessing metabolic potential, EPA considers established principles of xenobiotic metabolism as well as any available metabolism studies on chemical analogues (3,7,8). Potential metabolites are then subjected to analogue search and literature search as described above.

The successful application of this component requires the experience and judgment of scientific assessors in interpreting and integrating the available information. In evaluating the use of different analogues, the assessor considers the similarity of the analogue to the PMN chemical. This assessment is performed using a variety of factors that include comparisons of physical chemical properties, absorption potential, metabolic potential, the presence and positioning of reactive functional groups, and possible mechanisms of toxicity. Metabolites are evaluated in terms of the likelihood and significance of their formation. For example, if a postulated metabolite is projected to require a series of biotransformation steps for its formation or can be formed only via an unusual or theoretical pathway, these points will be considered in reaching assessment conclusions.

Use of QSARs

The third component entails the use of QSARs, which are used extensively in assessing the hazards of chemicals lacking adequate data. At this time, however, the use of QSARs is limited to estimating certain physicochemical properties (9), ecological toxicology, and fish bioconcentration factors (10). EPA/OTS approaches in estimating the latter two items are discussed below.

A QSAR is a quantitative relationship between chemical structure and a specific biological effect and is derived using information on a series of related chemicals (11). The chemical structure component can include one or more structural or physicochemical attributes, while the activity component can include any measurable effect or biological fate attribute observed following acute or chronic exposure to a chemical. For example, a common effect is acute toxicity to fish, often expressed as the 96-hr LC_{50} (the aqueous concentration needed to kill 50% of a population within 96 hr). A common biological fate attribute is the bioconcentration factor (BCF), which is the equilibrium concentration of a chemical in an organism following aqueous and/or oral exposure. Statistical methods are used to determine the relationship between structural attribute(s) and effect. Regression analysis is one of the more frequently used methods and has been relied on extensively by the EPA/OTS in developing QSARs. The predictive power of a QSAR varies with the amount of data, the mode(s) of toxic action, and any interactions between the modes of toxic action and bioavailability. Driven by assessment and regulatory needs under the various sections of TSCA, EPA/OTS has developed QSARs based on as little as one datum and assumptions about the nature of the relationship between a chemical class and its toxicity.

However, EPA/OTS prefers to use QSARs that are based on as much data as possible and, accordingly, new data are added whenever they become available.

In theory, a variety of physicochemical properties have been used to develop QSARs including octanol/water partition coefficient (K_{ow}); hydrophobicity; hydrophilicity; degree of dissociation of an ionizable functional group (pK_a); chemical reactivity; steric attributes such as molecular size, molecular volume, and molecular shape; hydrophile-hydrophobe balance; and surface tension (9,12-15). In practice, however, given the unavailability of environmental testing results on most industrial chemicals, the EPA/OTS has relied on those structural and physicochemical properties that can be easily determined from chemical structure, i.e., K_{ow} ; molecular weight (MW); number of carbons in the hydrophobic alkyl chain of a surfactant and/or number of ethoxylate units in a surfactant; and charge density of polycationic polymers (e.g., percent of amine-nitrogen, or more generally, the number of cationic charges per unit MW).

EPA/OTS uses QSARs extensively in the environmental hazard assessment of new chemicals. Clements et al. (10) presented 49 QSARs currently used by EPA/OTS to predict the toxicity of industrial organic chemicals to aquatic organisms. These QSARs apply to about 40 classes and subclasses of organic chemicals and are grouped into three broad types based on the mode of toxic action: neutral organic chemicals that are assumed to act with a narcotic mechanism; organic chemicals that are assumed to have a more specific mode of toxic action and show excess toxicity in addition to narcosis; and organics that are surface active agents. In addition, there are a number of chemical classes where EPA/OTS

has tried but not succeeded in attempts to develop environmental toxicity QSARs.

Neutral Organic Chemicals

Neutral organic chemicals are nonelectrolyte and non-reactive compounds (e.g., solvents) that act like anesthetics or narcotics. Descriptions of narcotic toxicity can be found in Lipnick (16), Franks and Lieb (17), and Veith and Broderius (18) in these proceedings. Classes of organic chemicals having neutral organic QSARs according to Clements et al. (10) include: alcohols, ketones, ethers, alkyl halides, aryl halides, aromatic hydrocarbons, aliphatic hydrocarbons, sulfides, and disulfides. There are nine QSARs for the neutral organic chemical class and most of these QSARs are effect specific (e.g., 96-hr LC_{50} , 16-day EC_{50} , and fish BCF). In general, QSARs are specific with respect to the effect modeled, but may or may not be specific with respect to species (e.g., the QSAR for fish BCF includes data from 15 species). Excellent predictive power can be obtained using K_{ow} alone.

Chemicals Having Excess Toxicity

Organic chemicals with a more specific mode(s) of toxic action may contain reactive functional groups (e.g., groups known to be electrophilic or nucleophilic that act directly or following metabolic activation (16); ionizable functional groups (e.g., phenols and anilines); specific structural attributes having specific toxic mechanisms (e.g., acetylcholinesterase inhibition by alkyl phosphate esters); and/or any number of specific structural and mechanistic attributes. What distinguishes these classes of chemicals is that when toxicity test results are compared with toxicity values predicted by neutral organic (narcotic) QSARs, each of these classes of chemicals exhibit toxicity greater than that predicted by the narcotic QSARs (the EPA/OTS currently considers the latter to represent baseline toxicity for aquatic organisms). Chemical classes having excess toxicity include: acrylates, methacrylates, aldehydes, anilines, benzotriazoles, esters, phenols, and epoxides. Each chemical class in this group has its own QSAR (10) and, it is assumed, its own specific mode(s) of toxic action in addition to narcosis. However, just what these specific toxic mechanisms may be is presently poorly understood. For example, acrylates are known to be more toxic to fish than predicted by the neutral organic QSARs, but the cause of this excess toxicity is not known exactly. Russom et al. (19) and Reinert (20) discussed six possible toxic mechanisms for acrylates. Furthermore, Veith et al. (21) did not discuss a specific mechanism for the excess fish toxicity observed for simple esters, although a form of narcosis may be associated with monoesters as suggested by Veith and Broderius (18) in these proceedings. This suggests that knowing the mode of toxic action for a chemical class is not necessary for QSAR analysis. Selecting the proper QSAR for a given chemical is, however, a crucial element in

SAR analysis; the factors considered in making such judgments are discussed at a later point in this paper and by Clements et al. (10). Currently, only K_{ow} is used to predict aquatic toxicity for this group of chemicals, even though it is known that the predictive power of these QSARs could be improved by adding a second physicochemical attribute, e.g., reactivity, ionization constant (pK_a), or steric descriptor. However, EPA/OTS in its evaluation of new chemical is limited to those physicochemical attributes that can be easily predicted from chemical structure alone and, outside of laboratory experimentation, there are currently no easily utilized methods for predicting these descriptors directly from chemical structure.

Surface-Active Agents

The last broad group of QSARs (10) are those for surface active agents (i.e., chemicals that damage the respiratory membranes of aquatic organisms), and this group is composed of two subgroups: surfactants that can be absorbed through respiratory membranes and charged polymers that cannot be absorbed. While surfactants are thought to act primarily as surface-active agents during acute exposures by destroying respiratory (i.e., gill) membranes, it is assumed that they act primarily as systemic toxicants during chronic exposures because they can be absorbed through respiratory membranes. Charged polymers are thought to only act through a surface active toxic mechanism since their MWs (generally greater than 1000 amu) prevent them from being absorbed to a significant degree (22). Surfactant QSARs in Clements et al. (10) include anionic surfactants, specifically, linear alkyl benzene sulfonates (LAS); nonionic surfactants, specifically, alcohol ethoxylates and ethoxylated β -amine surfactants (ETHOMEEN); and cationic surfactants, specifically, linear *N*-alkyl quaternary ammonium compounds. The QSARs for all of these surfactants are parabolic, i.e., toxicity is related to the size of the hydrophobic component in a parabolic manner when the size of the hydrophilic component remains constant. The size of the hydrophobic component, usually a linear alkyl carbon chain, is estimated by simply counting the number of carbons in the hydrophobic alkyl chain. In all the surfactant QSARs used by EPA/OTS, maximum toxicity (or lowest effective concentration or EC_{50} value) occurs when there are about 16 to 17 carbons in the hydrophobic alkyl chain. Toxicity for the nonionic surfactants is also affected by the number of ethoxylate units, and this must be known before accurate predictions can be made.

The only QSAR for charged polymers is for polycationic polymers (polycationic polymers include polymers with primary amines, secondary amines, tertiary amines and/or quaternary ammoniums, polyphosphoniums and polysulfoniums). The mode of toxic action for these polymers is specifically surface activity, in that they are known to destroy the respiratory membranes of aquatic organisms (unpublished observations from EPA/OTS New Chemical Review Program, Washing-

ton, DC). The molecular descriptor used to predict toxicity for these polymers is equivalent charge density as determined from chemical structure, i.e., percent amine-nitrogen or number of cationic charges per 1000 MW. If the polymer is based on nitrogen moieties that can be protonated and/or are quaternarized, then percent amine-*N* or number of cationic charges per 1000 MW can be used as a molecular descriptor. In a similar fashion, if the cations are based on polyphosphoniums or polysulfoniums, the number of cationic charges can also be used. These QSARs are appropriate for use when the number average MWs are over 1000 amu (i.e., the mode of the distribution of MWs is greater than 1000); in addition, polymers must be water soluble and/or dispersible. These QSARs are biphasic with toxicity increasing exponentially with charge density from 0.1 to 2.4 cations/1000 MW, thereafter becoming asymptotic.

Some Chemical Classes Lacking QSARs

EPA/OTS has no QSARs for polyanionic polymers, cationic dyes, acid dyes, inorganic chemicals, and for most classes of pesticides. Two classes of polyanionic polymers are known to be toxic to aquatic organisms: poly(aromatic sulfonic acids) that are most toxic to fish and polycarboxylic acids that are toxic only to green algae. These polymers are not expected to be absorbed due to their high MWs and are assumed to be surface active in their toxic mechanism, but anionic charge density is not correlated to toxicity (unpublished observation of EPA/OTS New Chemical Review Program) and no other meaningful molecular descriptors are known.

Cationic dyes are toxic to aquatic organisms and, like surfactants, are probably primarily surface active agents during acute exposures but primarily systemic toxicants during chronic exposures since they can be absorbed. Attempts have been made to relate effective concentrations for aquatic organisms within subclasses of cationic dyes (R. D. Platz, E. W. Odenkirchen, and J. V. Nabholz, unpublished observations). It has been hypothesized that dyes with delocalized cationic charges are more toxic, followed by dyes with four localized charges, then three localized charges, etc. However, correlations were weak and as more dyes were included in the analysis the relationship became progressively worse. The most probable explanation is the intrinsic impurity of commercial dyes. All of the dyes analyzed were commercial dyes with varying amounts of impurities, which is typical of dyes submitted under TSCA, Section 5. While a strong correlation might be observed if pure dyes were tested, too much inherent variability exists in commercial dyes for QSAR analysis. As a result, each such commercial cationic dye has to be tested to determine its aquatic toxicity.

Acid dyes are toxic only to green algae (J. V. Nabholz, unpublished observations). Analysis of available data suggested that effects to algae were not direct effects of the acid dye but represented indirect effects from shading. Perez et al. (23) partially confirmed this con-

while studying the effects of the blue acid dye, Direct Blue 15, in a site-specific marine microcosm. It appeared that the potency of the indirect effect was related to the color of the dye and the intensity of light shading. Therefore, blue dyes should have a stronger effect than orange or yellow dyes, and deep blue dyes should have a stronger effect than light blue dyes. EPA/OTS has not been able to test this hypothesis because absorption maxima are generally not included in PMN submissions and because of the difficulty of predicting light absorption from chemical structure. In practice, light absorbance attributed to dye color and intensity for a series of acid dyes will have to be measured concurrently with toxicity studies if any QSAR is to be developed.

Factors To Be Considered in Selecting and Evaluating a QSAR

Prior to using a QSAR, specific information must be gathered about a chemical so that the proper model can be identified and selected. The major factors considered by EPA/OTS (10) in conducting a QSAR-based analysis of a poorly studied chemical include chemical class, K_{ow} , MW, physical state and water solubility, number of carbons and/or ethoxylates, and percent amine-nitrogen and/or number of cationic charges per 1000 MW. These factors are discussed in detail by Clements et al. (10); they are set up as a user-directed guide to the proper selection and use of the available QSARs.

The initial determination of chemical class is probably the most important, because QSARs currently are chemical class specific. Clements et al. (10) have an alphabetical listing of chemical classes for which there are QSARs. Users simply find the chemical class to which the compound in question belongs and identify the proper QSAR.

QSARs for neutral organic chemicals, which act as narcotics, and chemicals with excess toxicity are based on K_{ow} . QSARs predicting acute toxicity to aquatic organisms (96-hr LC_{50} values) are valid when $\log K_{ow}$ values are less than five. When organic chemicals have $\log K_{ow}$ values of greater than five, then longer exposures are necessary to attain 50% lethality. If $\log K_{ow}$ exceeds eight for a chemical, no adverse effects are expected at saturation even under long-term exposures. QSARs for chronic (long-term) exposure (greater than 20 days for daphnids and the early life stages of fish, and 4 days for green algae) are valid for $\log K_{ow}$ values of eight or less (10).

QSARs for organic chemicals that show excess toxicity are generally valid for $\log K_{ow}$ values of about five or less. Excess toxicity decreases with increasing $\log K_{ow}$ until it becomes indistinguishable from baseline (narcotic) toxicity at about a $\log K_{ow}$ of five. This pattern has been demonstrated for esters by Veith et al. (21); epoxides by Deneer et al. (24); acrylates and methacrylates by J. V. Nabholz and R. D. Platz (unpublished observations) and Russom et al. (19); aldehydes by Deneer et al. (25) and R. G. Clements and J. V. Nabholz

(unpublished observations); and benzotriazoles by J. V. Nabholz (unpublished observations).

MW is needed to convert moles/L to mg/L since most QSARs are generally determined based on a moles/L basis. In addition, MW is used to set absorption cutoffs for aquatic organisms. Absorption through biological membranes is considered possible for molecules with MWs of less than 600 (22); absorption decreases significantly with MWs greater than 600. Chemicals with MWs of greater than 1000 are assumed to have negligible (i.e., biologically insignificant) absorption. For surface active compounds, there is no MW limit since toxicity from surface active compounds does not require absorption.

A determination of physical state (liquid, solid, or gas) for a compound is important for a proper QSAR application. QSARs used by EPA/OTS were developed almost entirely on organic chemicals that are liquids at room temperature. If an organic chemical is a solid at room temperature, then the melting point needs to be known or estimated because of the effect it has on water solubility, i.e., assuming K_{ow} is constant, the higher the melting point of a neutral organic chemical, the lower its water solubility (26). Whenever EPA/OTS predicts the aquatic toxicity for an organic chemical using QSARs, regardless of its physical state, the predicted effective concentration is compared with the water solubility. When the effective concentration is significantly higher than the measured or predicted maximum water solubility, then the effect is not expected to occur. In practice, prediction of water solubility and/or dispersibility in water is often difficult to obtain from chemical structure. In many cases, water solubility and dispersibility are considered essentially synonymous.

The number of carbons and/or ethoxylate units in an organic compound is needed only when the compound is expected to act like a surfactant, and a surfactant QSAR is to be used to predict aquatic toxicity. All of the surfactant QSARs used by EPA/OTS are based on surfactants where the hydrophobic component is composed of a single aliphatic carbon chain and/or linear chains of ethoxylate units. Surfactants that have complex hydrophobic components are assessed by calculating the K_{ow} of the complex hydrophobic component alone and determining which aliphatic alkyl (carbon) chain has an equivalent K_{ow} . Toxicity predictions are based on this equivalent chemical structure. Finally, the need to calculate the percent amine-nitrogen and/or number of cationic charges per 1000 MW is necessary when the toxicity of a polycationic polymer (10) is to be predicted.

Illustrative PMN Hazard Assessments

As discussed above, the first step in EPA/OTS analysis of the potential hazards of new chemicals involves critical analysis of any submitted test data. Given the prevailing circumstances of limited test data, however,

EPA/OTS has come to rely on an SAR approach, as described above, to supplement available data and to support the development of scientific evaluations of the potential hazards posed by data-poor chemicals. The goal of EPA/OTS PMN hazard analysis is to identify and assess the potential hazards and then to determine the further testing that is needed to permit an adequate assessment of the chemical. It is important to recognize that while SAR is being used by the Agency as an assessment tool, SAR approaches are not viewed as a replacement for test data. When one is dealing with data-poor chemicals, however, EPA believes that SAR can be a useful tool in evaluating the potential hazards of such chemicals and for identifying assessment or testing needs and priorities. Examples of several PMN hazard assessments follow and can serve to illustrate EPA/OTS application of the approaches described above. The first two examples focus on assessment of human health hazards, while the balance of the examples are focused on assessment of environmental effects. Note that although the examples are limited to discussion of either health or environmental effects, in practice under the new chemicals program EPA/OTS assesses both health and environmental effects for all PMN chemicals submitted to the agency. Statements not supported by references represent the assessment of EPA/OTS scientists.

Health Hazard Assessments

Example 1: An Azo Dye. This PMN chemical (I; Fig. 2) is intended for use as a dye for fabric. Submitted toxicological data were as follows: rat oral $LD_{50} > 5$ g/kg; rabbit dermal $LD_{50} > 2$ g/kg; mild eye irritant in the rabbit; Salmonella/microsome assay (Ames Test), positive with or without activation; mouse lymphoma L5178Y assay, positive with or without activation.

HAZARD ASSESSMENT. PMN chemical I, a lipophilic azo dye, was expected to be absorbed via the gastrointestinal tract and lungs and to a lesser extent via the skin. If absorbed intact, chemical I may be subject to reductive cleavage in the liver which would release 5-nitro-2-aminothiophene (II; Fig. 2) and a substituted para-phenylenediamine (III; Fig. 2). In addition, the dye was subject to azo cleavage in the gut by intestinal flora (27). If azoreduction occurred in the gut, metabolites II and III would be more readily absorbed systemically than the parent compound. Wang et al. (28) pointed out the great similarity in structure and chemical properties between 5-nitrofurans and 5-nitrothiophenes and discussed the metabolism of these compounds. Both 5-nitrofurans and 5-nitrothiophenes appeared to undergo nitroreduction and binding to macromolecules; activation and binding was proposed to involve formation of a free radical or nitroso derivative.

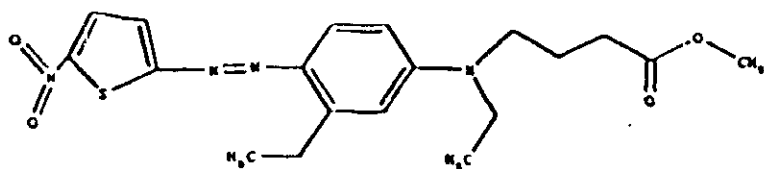
Submitted genotoxicity data indicated that the chemical was mutagenic *in vitro* (the Ames Test response was 20 × background with activation). Numerous 5-nitrofurans and 5-nitrothiophenes have been demonstrated to be mutagenic in the Ames Test (29,30), and

many of these compounds are also known to be carcinogenic (29,31). Arcos and Argus (32) discussed the importance of the nitro group and the influence of aryl substitution on the carcinogenic activity of 5-nitrofurans. The authors noted the marked aromatic behavior of furan and that the aryl group at the 2-position is conjugated with the nitro in position 5 on the ring. Removal of the nitro group abolished activity.

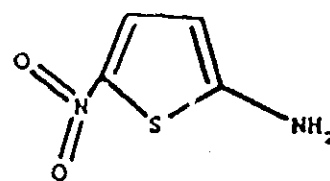
Aryl conjugated 5-nitrothiophenes possess carcinogenic potential similar to that of the 5-nitrofurans; this was confirmed in studies performed on a series of 5-nitrothiophenes (including IV and V depicted in Fig. 2) by Cohen et al. (29). No statistically significant increase in tumor incidence was reported for the thiophene compound (VI; Fig. 2) lacking the nitro group. Finally, results for compound VII (Fig. 2), which contained a conjugated intercylic vinyl moiety, indicated that the nitrofurans ring and the second aromatic ring need not be directly connected for the compound to be carcinogenic (29).

Based on the submitted evidence of mutagenic activity plus the discussion developed above regarding the carcinogenic potential of 5-nitrothiophenes and the analogous 5-nitrofurans, the PMN chemical was concluded to be mutagenic and was judged likely to be carcinogenic. Accordingly, it was recommended that, if exposures were significant, the PMN chemical should be tested in a lifetime animal bioassay to determine its carcinogenic activity.

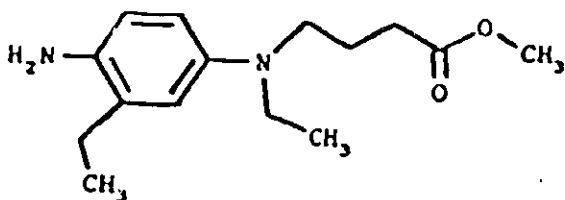
ANALOGUE SEARCH. The Structure and Nomenclature Search System in the Chemical Information System (SANSS/CIS; CIS, Inc., Baltimore, MD) was used in the analogue search described for this case. Three query structures (VIII, IX, X), were developed and used in the SANSS/CIS substructure search and are shown in Figure 3. Query structure VIII simulated chemicals analogous to the intact PMN chemical and allows the identification of both thiophene and furan analogues (i.e., 5-nitro(thiophene/furan)-2-yl azo compounds). Query structure IX identified thiophene/furan analogues of I that have an aromatic substituent at position 2, while query structure X identified analogues having an intercylic vinyl moiety at position 2. After the search with the query structures was completed, the search results were intersected with a selected subset of the pointers in SANSS/CIS to assist and speed the analogue identification process. [Pointers in SANSS/CIS are used to identify or point to specific data files or information sources (e.g., computerized databases, secondary reference works, etc.), which are indexed by chemical in the information system.] In this example, a carcinogenicity/genotoxicity pointer file was created in SANSS/CIS by merging the chemicals included in the following pointer files: International Agency for Research on Cancer, Monographs on the evaluation of the carcinogenic risk of chemicals to humans (33); U.S. Public Health Service, survey of compounds that have been tested for carcinogenic activity (34); and GENETOX, a genetic toxicity data base developed by EPA (35,36). In a similar fashion, pointer



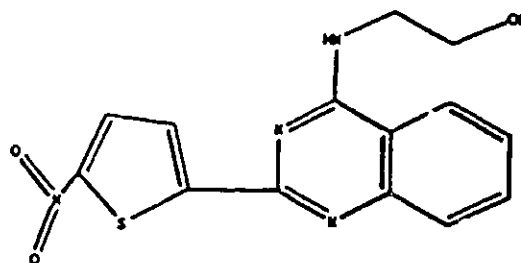
I



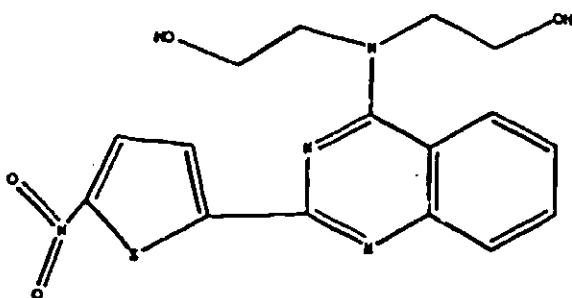
II



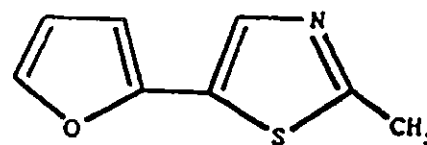
III



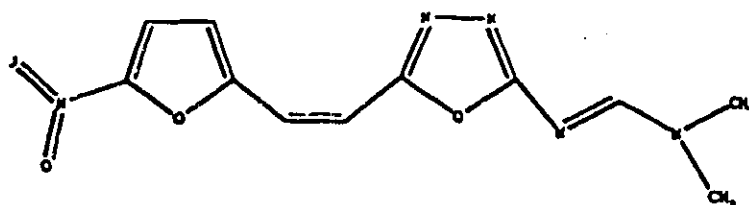
IV



V



VI



VII

FIGURE 2. Chemical structures cited in Example 1.

files for other end points (general toxicity, aquatic toxicity, etc.) can also be set up and be used in SANSS/CIS. The results of the intersection of the substructure search files for the three query structures with the entire SANSS/CIS data base and the carcinogenicity/genotoxicity pointer files are shown in Table 2 (note that double counting has not been excluded).

The output from the query structure searches was examined to identify chemicals that had the greatest similarity to the PMN chemical (considering the factors described earlier) and that appeared to have carcinogenicity/genotoxicity test data available (as shown by SANSS/CIS pointers). The potential analogues that best met the needs of the review were selected and then

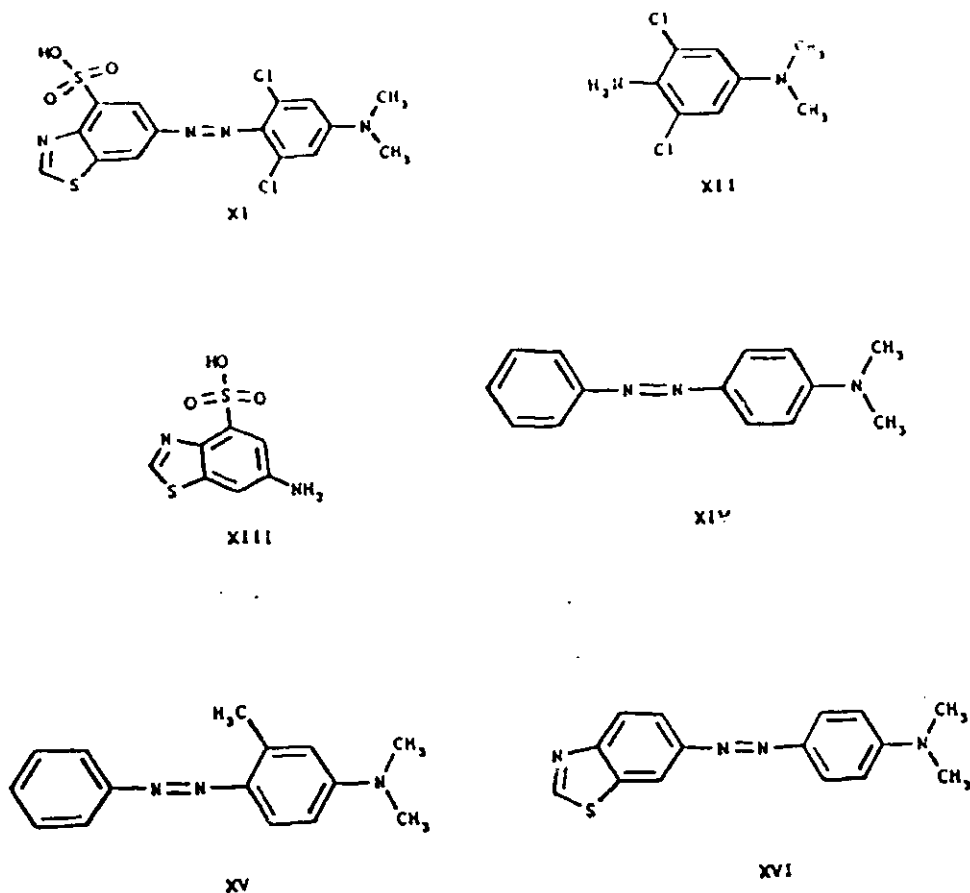


FIGURE 3. Query structures cited in Example 1. R = S or O. X = Any aromatic moiety.

Table 2. Results of intersecting the substructure search files with the SANSS/CIS data base and the carcinogenicity/genotoxicity pointer files:

Pointer files	Number of chemicals		
	VIII	IX	X
Query structure	3	10	19
Total SANSS/CIS hits	0	6	7
Carcinogenicity/genotoxicity file hits			

subjected to a literature search to identify possibly relevant articles. Note that query structure VIII did not yield any data-containing analogues.

Example 2. An Azoheterozole. The PMN chemical (XI; Fig. 4) was a monoazo compound. No toxicological data were submitted by the manufacturer and the intended use of the chemical was claimed confidential business information by the submitter.

HAZARD ASSESSMENT. Little or no absorption of the PMN chemical was expected through the skin, while some absorption of the chemical was expected in the lungs and gastrointestinal tract. Azoreduction was expected to occur in the gastrointestinal tract (27), releasing the individual monocyclic (XII; Fig. 4) and heterocyclic (XIII; Fig. 4) moieties of the chemical. The azoreduction products of the PMN chemical were expected to be more readily absorbed (especially metabolite XII) than the intact chemical. Sulfonation of the

PMN chemical increased its water solubility, which was expected to increase the extent of azoreduction in the gastrointestinal tract and to reduce absorption of the intact molecule and metabolite XIII.

The PMN chemical was identified as a prime ring analogue of *N,N*-dimethylaminoazobenzene (DAB; XIV; Fig. 4), a potent hepatocarcinogen (37), and derivatives thereof. One derivative of DAB, 2-methyl-DAB (XV; Fig. 4), has been shown to be carcinogenic only following partial hepatectomy and dietary administration of the chemical (38). The chemical 6-*p*-dimethylaminophenylazobenzothiazole (6-BT; XVI; Fig. 4), a close structural analogue of the intact PMN chemical, has also been shown to be a potent rodent hepatocarcinogen (39,40).

DAB and 6-BT both produced positive responses in mutagenicity assays with *Salmonella* (41). In addition, 6-BT produced positive results in an *in vivo* rat liver unscheduled DNA synthesis (UDS) bioassay (42).

It has been demonstrated that MAB (the monomethyl analogue of DAB) binds to DNA as an intact moiety (43). Bioactivation of DAB has been suggested to involve *N*-demethylation followed by *N*-oxidation and conjugation of the derived hydroxylamine to form a reactive species capable of binding to DNA (44). A similar activation mechanism has been proposed for 6-BT (45).

The carcinogenicity of DAB is known to be reduced

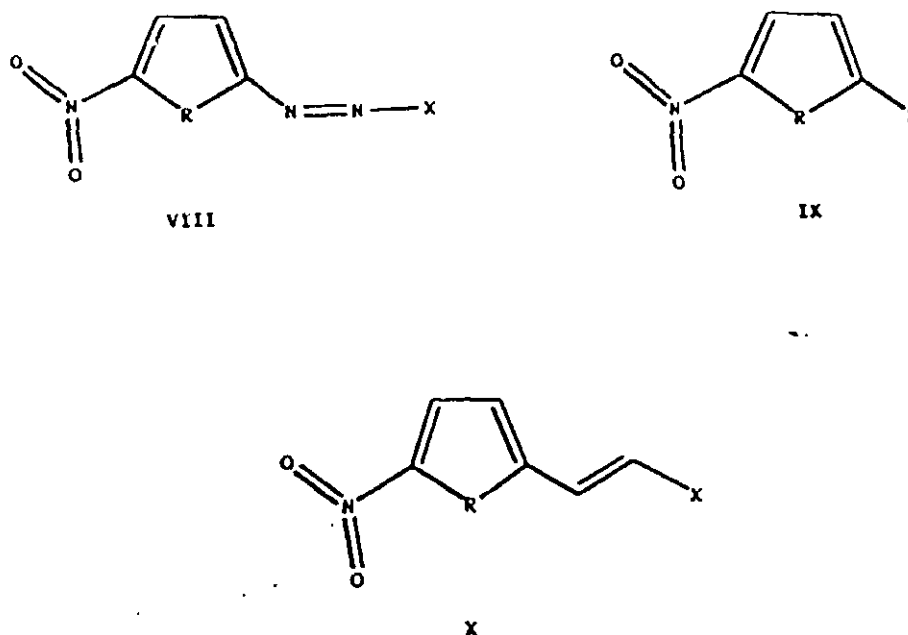


FIGURE 4. Chemical structures cited in Example 2.

by diets high in riboflavin content (Vitamin B₂), and reduction in carcinogenic activity has been attributed to an increase in azoreduction activity (46). Azoreduction of 6-BT was reduced by 90% in rat liver tissue when the rats were placed on a low riboflavin diet (47). It has also been shown that the azoreduction products of 6-BT were nonmutagenic in *Salmonella* (48). Although the phenylene diamine portion of the PMN chemical has substituents not found in DAB or 6-BT, no data were available to suggest that metabolite XII may be potentially carcinogenic; on the contrary, 2,6-substitution on DAB may be inferred to eliminate or minimize carcinogenic potential (37).

Miller et al. (37) proposed that for DAB and analogues thereof to be carcinogenic, the 2-position must be unsubstituted. These authors demonstrated that when the 2-position and the equivalent 6-position of DAB were substituted with fluorines, carcinogenic potential was lost, based on results observed with 1-year studies on 3 fluorinated derivatives of DAB. 2-Methyl-*N*-methyl aminoazobenzene was found to be, at best, weakly carcinogenic (1/16 animals had a liver tumor at 11 months). Arcos and Argus (38) proposed that all carcinogenic azo compounds were probably *trans* and coplanar, and that bulky ring substituents *ortho* to the azo linkage disrupted this configuration. Since coplanarity and conjugation across the molecule were believed to be important factors in the carcinogenicity of DAB-type compounds and substitution at the 2-position disrupted this configuration, it was possible that the PMN chemical, which was halogenated at the 2,6-position, would exhibit minimal activity, relative to DAB.

Overall, there was a concern for the carcinogenic potential of the PMN chemical based on structural analogies to DAB and 6-BT. The concern for carcinogenic

potential was mitigated by evidence that 2,6-substitution was likely to reduce or eliminate carcinogenic activity; a lack of evidence suggesting the azoreduction products of XI were likely to be carcinogenic; and estimates that only limited absorption of the intact PMN chemical would occur. However, since evidence for the low carcinogenic potential of 2,6-disubstituted analogues of the PMN chemical was based on less-than-lifetime studies, it was recommended that if exposure potential was sufficient, genotoxicity tests (Ames test and an *in vivo* mouse micronucleus assay) should be performed on the PMN chemical. 6-BT should be used as a positive control in both assays. The results obtained with the PMN chemical would be evaluated independently and compared with those obtained with 6-BT to test the analogy between the two substances. If results of these assays were positive, and especially if the results were qualitatively consistent with those for 6-BT, an oncogenicity bioassay should be performed.

Environmental Effects Assessments

Example 3. An Aliphatic Ketone. The PMN chemical (XVII; Fig. 5) is intended for use as a solvent for paints. No environmental toxicological data were submitted by the manufacturer, however, the following physical/chemical properties were listed: $\log K_{ow} = 2.9$ at 20°C; molecular weight, 142; water solubility, 714 mg/L at 20°C; and liquid at room temperature.

HAZARD ASSESSMENT. The PMN chemical is non-reactive and is a nonelectrolyte. It is expected to exhibit only narcosis (and thus baseline) toxicity to aquatic organisms and is expected to be easily absorbed from water. Toxicity predictions based on the neutral organic QSARs (in mg/L) are as follows:

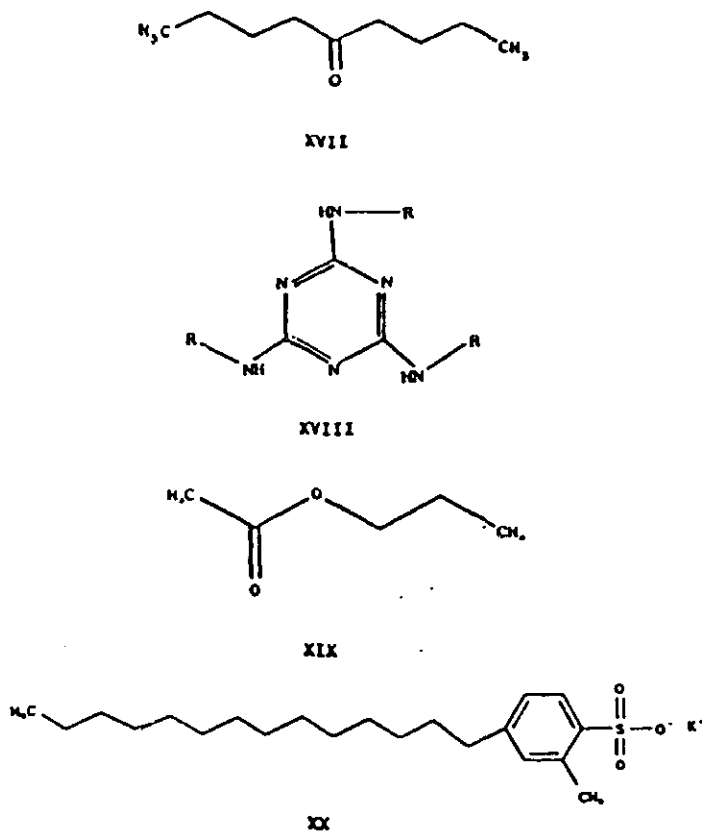


FIGURE 5. Chemical structures cited in Examples 3-6. For structure XVIII, R = linear or branched aliphatic ethers and alcohols.

Freshwater green algae 3-hr EC ₅₀ for inhibition of photosynthesis	> 10,000.0
Freshwater fish 14-day LC ₅₀	31.0
Daphnid 48-hr LC ₅₀	17.0
Freshwater fish 96-hr LC ₅₀	16.0
Freshwater green algae 96-hr LC ₅₀ for growth inhibition	7.7
Marine fish 96-hr LC ₅₀	5.0
Daphnid 16-day LC ₅₀	3.6
Mysid shrimp (marine) 96-hr LC ₅₀	2.2
Daphnid 16-day LC ₅₀ for reproductive inhibition	1.3
Freshwater green algae 96-hr no effect concentration (NEC)	1.9

[NEC is equivalent to the chronic value (ChV) or the geometric mean of the maximum allowable toxicant concentration (GMATC); the MATC is the range of concentrations between the no-observed-effect concentration (NOEC) and the lowest-observed-effect concentration (LOEC).] The 28-day BCF for fish is predicted to be 79.

All of the QSARs, except for the 96-hr EC₅₀ and NEC for freshwater green algae, used in the analysis came from Clements et al. (10); the algal 96-hr ECs came from a QSAR developed from Calamari et al. (49), and it is a future addition to Clements et al. (10) when it is revised.

The QSAR-based toxicity profile for aquatic organisms indicates that toxicity is not limited by water sol-

ubility; marine fish and invertebrates (i.e., mysid shrimp) are slightly more sensitive than freshwater fish and invertebrates (i.e., daphnids); and freshwater green algae appear to be more sensitive than freshwater fish and invertebrates. Note, however, that the 96-hr bioassay for green algae is actually a chronic toxicity test relative to algae because this test is multi-generational (i.e., 96 hr allows for the attainment of exponential growth and the production of about eight generations of algae) and the effect is a sublethal effect, i.e., inhibition of population growth. Also, the algal 96-hr EC₅₀ and NEC values compare closely with the daphnid 16-day LC₅₀ and EC₅₀ values that are estimates of chronic toxicity for daphnids. Overall, this solvent is considered only moderately toxic to aquatic organisms because the base set of toxicity values (i.e., fish 96-hr LC₅₀ values, aquatic invertebrate acute LC₅₀ values and the algal 96-hr EC₅₀ values) are between 1 and 100 mg/L. Finally, concerns for the bioconcentration potential of this solvent are low because the fish BCF is less than 250, and the BCF values for aquatic invertebrates and algae are expected to be equal to or less than the BCF for fish.

Example 4. A Substituted Melamine. This PMN chemical is a substituted melamine (XVIII; Fig. 5) containing various branched and linear aliphatic ethers and alcohols. Its use was claimed confidential by the manufacturer. The following data were submitted with the PMN:

Average number MW	= 1300
Percent < 1000 MW	= 20%
Percent < 500 MW	= 10%
Water solubility	= 0.300 mg/L (measured)
Freshwater fish 24-hr LC ₅₀	= 50 mg/L
Freshwater fish 96-hr LC ₅₀	= 20 mg/L
Freshwater fish 96-hr LOEC	= 10 mg/L
Daphnid 24-hr LC ₅₀	> 100 mg/L
Daphnid 48-hr LC ₅₀	= 90 mg/L
Daphnid 48-hr NEC	= 42 mg/L
Freshwater green algal 96-hr NOEC	= 0.300 mg/L
Liquid at room temperature	

Toxicity test data were based on 100% active ingredient, static aqueous exposures where a carrier solvent and dispersant were used for dissolution, and nominal (i.e., unmeasured) toxicant concentrations.

HAZARD ASSESSMENT. The PMN chemical is non-reactive and is a nonelectrolyte. It is expected to exhibit only narcosis and baseline toxicity to aquatic organisms and is not expected to be easily absorbed from water because the MW is greater than 1000. QSAR analysis (10) indicated that this chemical should not exhibit any adverse effects at saturation; however, lethality to fish and aquatic invertebrates was observed during testing. Acute effective concentrations were higher than measured water solubility by at least 30 times. The algal toxicity test results were consistent with QSAR analysis. In this test, the maximum treatment concentration was at the limit of water solubility and no adverse effects were observed. It was concluded that the toxicity seen in the acute fish and aquatic invertebrate tests

ld not be attributed to the carrier solvent and dispersant because these carriers were also present in the algal bioassay, and algae are generally more sensitive to dispersants than fish and daphnids. If no toxicity data had been submitted with the PMN, EPA would not have identified concerns for potential hazard to the aquatic environment. However, since effects were observed during the acute toxicity tests with fish and aquatic invertebrates and it did not appear to be due to the carriers, it was recommended that chronic testing with daphnids and fish be done with the highest treatment concentration set at 300 μ /L or the maximum water solubility, if higher.

After consultation with EPA/OTS, the submitter conducted a fish 14-day toxicity test at 1 mg/L (the apparent maximum water solubility under testing conditions) without any carriers. Test conditions included flow-through conditions with measured concentrations and 100% active ingredient. In addition, the submitter also tested the carriers in fish acute toxicity tests. The results of these tests were no observed effects at saturation during the fish 14-day toxicity test and very low toxicity (i.e., acute values greater than 1000 mg/L) for the carriers. Since these test results were consistent with the EPA/OTS hazard assessment, no additional steps were taken with the PMN chemical.

This example illustrates how QSAR analysis can assist in interpreting and validating environmental toxicological testing results and also demonstrates EPA/OTS belief that SAR analysis, while of great value, is not to be relied upon as a substitute for test data. Another important point to recognize is that testing such as that conducted under EPA/OTS New Chemical Review Program can subsequently be used to improve EPA/OTS SAR predictions.

Example 5. A Simple Ester. This PMN chemical is propyl acetate (XIX; Fig. 5). Its use has been declared confidential business information by the manufacturer. No environmental toxicological data were submitted by the manufacturer, however, the following physical/chemical properties were listed: purity, 99%; MW, 102; melting point, -59°C ; density, 0.888 mg/mL at 20°C .

HAZARD ASSESSMENT. The PMN chemical is a non-electrolyte but is expected to be more toxic than what would be predicted from the neutral organic (narcotic) QSARs (at least in some species) as has been shown with other simple esters (21). The log K_{ow} was calculated to be 1.2 using the computer program, CLOGP, Version 3.3 (50). Toxicity (in mg/L) and BCF predictions based on QSAR analysis are as follows:

Daphnid 48-hr LC_{50}	425.0
Green algal 96-hr EC_{50} for inhibition of growth	200.0
Green algal 96-hr NEC for growth inhibition	50.0
Fish 96-hr LC_{50}	41.0
Daphnid 16-day LC_{50}	32.0
Daphnid 16-day LC_{50} for reproductive inhibition	15.0
Fish BCF	3.0

All of the QSARs, except for the toxicity values for green algae came from Clements et al. (10); the algal predictions came from QSAR developed from Calamari et al. (49). The fish acute value, which was derived from the QSAR for simple esters (21) and cited in Clements et al. (10), exhibit the expected excess toxicity. Comparison to the neutral organic QSAR for acute toxicity for fish indicated that this ester is expected to be about 10 times more toxic than an equivalent neutral organic chemical with the same K_{ow} and MW (i.e., the fish 96-hr $\text{LC}_{50} = 419$ mg/L based on the neutral organic QSAR).

The QSAR predictions for daphnids were based on the neutral organic QSARs. This ester was not expected to show excess toxicity to daphnids. The support for this conclusion lies in analysis of the phthalate ester QSARs (10) for fish and daphnids. Phthalate esters are simple esters and were included in the simple ester QSAR for fish acute toxicity by Veith et al. (19). Therefore, when a fish toxicity prediction for a phthalate ester is needed, Clements et al. (10) direct the user to the ester QSAR. However, when the available acute and chronic toxicity data for phthalate esters for daphnids were compared to the acute and chronic toxicity predictions for daphnids using the neutral organic QSARs (J. V. Nabholz, unpublished observations), there was no evidence of excess toxicity. Accordingly, Clements et al. (10) direct the user to use the neutral organic QSARs for daphnid acute and chronic toxicity when toxicity predictions are needed for phthalate esters and other simple esters. Finally, no excess toxicity from simple esters and phthalate esters is expected for freshwater green algae as well, since the available empirical data for simple phthalate esters do not indicate excess toxicity for green algae when compared to neutral organic QSAR predictions (J. V. Nabholz, unpublished observations).

This toxicity profile for aquatic organisms indicates that: a) fish are expected to be the most sensitive species; b) the excess toxicity predicted for fish is because of some specific mode of toxic action unique to fish, e.g., fish may have some metabolic pathway that is especially sensitive to interference by esters and a pathway that aquatic invertebrates may not have; c) there is a high probability that this ester could be a cumulative toxicant in fish, i.e., the ratio of the 24-hr LC_{50} value divided by the 96-hr LC_{50} value is expected to be greater than two; d) this cumulative toxicity is expected to be because of an accumulation of damage or injury and not to bioconcentration (increasing residues in fish) of the chemical because the bioconcentration potential of this ester is very low (thus there is also a low concern for bioconcentration in fish); and e) the fish chronic value (i.e., the NEC or GMATC) is expected to be more than 10 times lower (i.e., more toxic) than the fish acute (96-hr) toxicity value because the cumulative toxicity ratio is expected to be greater than two. Overall, the concern for hazard to the aquatic environment is moderate because of the excess acute toxicity and the expected high degree of chronic toxicity in fish.

000088

Example 6. A Linear Alkyl Toluene Sulfonate (LTS). This LTS (XX; Fig. 5) is an anionic surfactant with 14 carbons in the alkyl chain (or the hydrophobic component). It is intended for use in laundry detergents and hard-surface cleaners. The following information was submitted with the PMN: formulated as potassium salt; miscible (or dispersible) in water; PMN to be sold as 50% dispersion in water; pH of product = 7.6; fish 56-day BCF = 14.

HAZARD ASSESSMENT. The PMN is an anionic surfactant and is analogous to linear alkyl benzene sulfonates (LAS). Toxicity predictions (in mg/L) were based on the LAS QSARs from Clements et al. (10) and are as follows:

Fish 96-hr LC ₅₀	0.31
Daphnid 48-hr LC ₅₀	0.31
Green algal 96-hr LC ₅₀ for inhibition of growth	0.16
Green algal 96-hr NEC for growth inhibition	0.11
Fish 28-day NEC for early life stages	0.05
Daphnid 21-day NEC for reproductive inhibition	0.05

The predicted toxicity values for the PMN surfactant are expected to be very close to the actual test data if the chemical were to be tested because the LAS QSAR is based on a homologous series of LAS surfactants and has high predictive power. Any differences in toxicity between a linear alkyl benzene sulfonate and a linear alkyl toluene sulfonate (i.e., differences due to the presence of the methyl group on the LTS benzene ring) are expected to be insignificant. This QSAR-based toxicity profile for aquatic organisms indicates that a) toxicity is not expected to be limited by water solubility or dispersibility; b) while freshwater green algae are predicted to be slightly more sensitive during exposures of 96-hr or less, daphnids are predicted to be more sensitive during longer exposures; c) damage to algal cell membranes and gill membranes in fish and daphnids is expected during the 48 to 96-hr exposures, but not during the longer term exposure (21 to 28 days) tests; and d) toxicity during chronic exposures to daphnids and fish is expected to be attributed to an accumulation of systemic damage or injury rather than accumulation of the PMN chemical in the body (i.e., body residues), because the bioconcentration potential has been shown to be low. Overall, the hazard concern for the aquatic environment is high because the base set of aquatic toxicity tests are predicted to have effective concentrations (EC₅₀ values) of less than one. As a result, acute and chronic toxicity testing was recommended for this PMN. The testing recommendations consisted of the fish acute toxicity test, the daphnid acute toxicity test, and the green algal toxicity test; and the fish early life-stage toxicity test and the daphnid chronic toxicity test, if triggered by the base set toxicity tests. Chronic toxicity testing would be required if the fish and/or daphnid acute toxicity values are less than 1 mg/L or if the fish and/or daphnid acute toxicity values are between 1 mg/L and 100 mg/L and there are indications of cumulative toxicity (i.e., the ratio of the fish 24-hr LC₅₀ value to

the 96-hr LC₅₀ value or the ratio of the daphnid 24-hr LC₅₀ value to the 48-hr LC₅₀ value is greater than two).

If test data are eventually obtained for this LTS, these data will be compared to the predictions obtained from the LAS QSAR and incorporated into the LAS QSAR in order to improve predictions for these anionic surfactants in the future.

Summary

The limited availability of test data on the majority of industrial chemicals and environmental contaminants confronting the U.S. EPA has resulted in the development by the Agency of SAR-based approaches for hazard analysis. The major components of the analysis (which were discussed and illustrated in detail in this paper), involved review of available test data; application of test data available on analogous substances or potential metabolites of the target chemical; and the use of QSARs to predict physical-chemical properties, environmental effects, and bioconcentration factors. A key aspect in the application of the latter two components is the experience and scientific judgment of assessors in interpreting and integrating the information; these are critical in identifying structural or functional analogues or in selecting appropriate QSARs. The identification of possible modes of toxicity is an integral part of the overall approach. In many cases, the available information does not extend beyond chemical structure and basic physical-chemical properties that can be calculated from structure. Thus, the importance is evident of the EPA/OTS of this workshop, with its emphasis on predicting modes of toxicity from chemical structural information.

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The article has been reviewed by the Office of Toxic Substances, U.S. EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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**CALCULATION OF MAXIMUM EXPECTED EMITTED
CONCENTRATION (MEEC)
FOR THE AQUATIC COMPARTMENT**

$$\text{ppm (in environment)} = \text{lbs/yr production} \times 8.9 \text{ E}^{-9}$$

This equation is derived from the following:

$$\text{ppm} = (\text{A})(\text{B})(\text{C})(\text{D})(\text{E})(\text{F})$$

where:

A=pounds/year production;

B=year/365 days;

C= day person/150 gallons

D= 1/(million persons-population of U.S.)

E= gallons/8.34 pounds

F= million

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Environmental Risk Assessment of New Chemicals Under the Toxic Substances Control Act (TSCA) Section Five

1993b

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ABSTRACT: The Toxic Substances Control Act (TSCA) allows for the regulation of new industrial chemicals if a chemical may present an unreasonable risk toward the environment, or if a chemical has significant exposure toward the environment. Risk assessment under TSCA Section 5 consists of the integration of the hazard assessment for a chemical with the chemical's exposure assessment.

The environmental-hazard assessment consists of identifying all of the effects of a chemical toward organisms in the environment, and toward the populations, communities, and ecosystems to which those organisms belong. Toxicity data for a chemical consists of effective concentrations (EC), which indicate the type of effect and the seriousness of that effect on a given organism at a known concentration of chemical. Effective concentrations can be based on test data or predicted using structure activity relationships (SAR). A collection of all of the ECs for a chemical is called a hazard profile or a toxicity profile. Environmental factors which reduce the inherent toxicity of a chemical (that is, mitigation factors), as well as enhancement factors that increase toxicity are taken into account when the hazard profile is developed.

The environmental-exposure assessment consists of predicting the environmental concentrations of a chemical from releases due to its production, processing, uses, and disposal. There are two types of exposure assessment most frequently used under TSCA: the Particle Stream Flow Method and the Probability Dilution Model (PDM) Method.

Environmental-risk assessment is done by using the quotient method. This method simply compares an EC or a concern concentration (CC) to the actual or predicted environmental concentrations (PEC). If the PEC is greater than the EC or CC, then you have a potential risk.

Case studies for several types of chemicals will be presented: neutral organic chemicals; organic chemicals with excess toxicity; anionic surfactants; nonionic surfactants; cationic surfactants; amphoteric surfactants; anionic polymers; nonionic polymers; polyanionic polymers; polyampholytic monomers; acid dyes; neutral dyes; cationic dyes; amphoteric dyes; alkyloxysulfanes; and metals.

KEY WORDS: Toxic Substances Control Act, premanufacture notification, environmental risk assessment, hazard profile, assessment factor, concern concentration, exposure assessment, quotient method, organic chemicals, polymers, structure activity relationships, surfactants, chelators, dyes, metals, organometallics

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The Toxic Substances Control Act (TSCA) Section 5

The Toxic Substances Control Act (TSCA 1984) was enacted in 1976 and provided for the regulation of industrial chemicals. Section 5 requires premanufacture reporting requirements for new chemicals. TSCA has several unique features that are applied to all new chemicals. The entire life cycle of a chemical—from production to disposal—is assessed. The United States Environmental Protection Agency (the Agency or USEPA) is allowed to collect needed information about a chemical and the burden of generating new information, testing, for example, is placed on the chemical industry rather than the Agency. TSCA is also unique because it places the burden of decision-making on the Agency, which must use whatever information is submitted by the manufacturers. Under Section 5, these decisions have to be made quickly, that is, in less than 90 days. The need to make these quick decisions resulted in the development of the SAR that is described in this paper. Structure activity relationships allow you to predict the environmental toxicity of a chemical from its chemical structure.

TSCA allows for the regulation of a new industrial chemical if there is an unreasonable risk toward human health or the environment; and it allows for testing if a chemical may present an unreasonable risk or has significant exposure toward humans or the environment.

Since publication of the TSCA Inventory of existing chemicals in July 1979, the Agency received 18 076 notices under Section 5 through the end of Fiscal Year (FY) 1990. 1/521 Premanufacture Notifications (PMN), 1662 Low Volume Exemptions, 522 Test Market Exemptions, and 1371 Polymer Exemptions. Under TSCA Section 5, the only information required with a notice is chemical identity, molecular structure, trade name, production volume, uses and amount for each use, by-products and impurities, human-exposure estimates, disposal methods, and any test data in the possession of the notifier. TSCA does not require any toxicity testing prior to submission of a PMN. As a consequence, the Agency receives toxicity data on less than 50% of all new chemicals submitted (Auer et al. 1990). While about 50% of PMNs have human health test data, less than 10% of PMNs have environmental toxicity test data. Most of these toxicity data consist of acute lethality test reports. Environmental toxicity studies listed in order of decreasing frequency are fish acute toxicity, acute toxicity on aquatic invertebrates, algal toxicity, aquatic chronic toxicity, and toxicity studies with terrestrial organisms.

Assessment Process for Section 5 Notices

After receipt of a Section 5 notice by the Agency, the first step of the process (USEPA 1986) is to determine if all the required information has been included in the PMN. The second step is a chemistry review to ensure that information submitted is consistent with itself and with the principles of chemistry. The third step is an initial hazard assessment or identification of potential effects to humans and environmental organisms (or experts). If the new chemical is determined to be of low hazard, it is dropped from further review if it has a production volume of less than 100 000 kg/year. If there is a concern for the toxicity of the chemical or if it has a significant production volume, then the exposure of the new chemical to humans and the environment is assessed. This exposure assessment consists of an exposure analysis meeting and two reports are generated: an engineering report and an environmental-exposure report. The exposure assessment identifies all of the potential releases of the chemical throughout its entire life cycle, that is, manufacture, processing, use, and disposal, and quantifies each release in kilograms per day. The engineering report estimates worker exposure at each stage of the chemical's life cycle and

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releases of the chemical to the environment from each relevant site. The environmental exposure report estimates the environmental concentrations of the new chemical and the dose to the general human population from each release site including methods of disposal. All of these meetings occur within the first two weeks after receipt of the PMN. Nabholz (1991) has a more detailed discussion of the exposure assessment process under TSCA.

These meetings are followed by an initial risk assessment/risk management meeting called the FOCUS Meeting. This meeting is chaired by a regulatory decision-maker and at this meeting the hazard and exposure assessments are integrated for the first time in the assessment process; this integration results in a risk assessment. If a risk is identified for the chemical, it is subjected to either a more in-depth assessment, which is called a Standard Review, or it is regulated directly out of the FOCUS meeting, usually with a requirement for testing. Those chemicals with no predicted risks or with reasonable risks are dropped from further review at FOCUS. If the Standard Review supports the risk assessment finding at FOCUS that a chemical is a risk to the environment, the case is presented to senior regulatory decision-makers in the Office of Toxic Substances (OTS). The results of the risk assessment as well as the economic and relative risk factors, such as the cost or benefits of the new chemical, the cost of any additional testing, the economic impact of testing or regulation on the submitter, and the relative exposures of the chemical compared to any substitutes, are discussed in order to decide whether a chemical presents an "unreasonable" risk to human health or the environment. The possible outcomes are: (1) control pending additional testing under TSCA Section 5c, (2) screening level testing requirements predicated on significant production and exposure or release, (3) issuance of a significant new use rule (SNUR) under TSCA Section 5, (4) direct control under TSCA Section 5f, or (5) no controls (that is, dropping the chemical from further review). All of these possible decisions depend on the strength of the case made for an "unreasonable" risk determination. A decision under TSCA Section 5c only requires a "may present" finding, while a decision under TSCA Section 5f requires a "will present" finding. If the case is so weak that neither of these findings can be made to the satisfaction of the senior regulatory decision-makers, the case is dropped from further review without any regulatory action or controls. A flow diagram of the assessment process under Section 5 is available in USEPA (1986).

Environmental Risk Assessment

Hazard Profile

The environmental hazard assessment of a new chemical consists of identifying as many of the effects of that chemical towards organisms in the environment as possible (Nabholz 1991). Toxicity data for a chemical generally consist of effective concentrations (EC) that indicate the type of effect and the seriousness of that effect at a known concentration of the chemical. A collection of the effective concentrations on a range of species for a chemical is called a Hazard Profile or Toxicity Profile. The most frequently encountered Hazard Profile for a new chemical consists of six effective concentrations:

- fish acute value;
- aquatic invertebrate acute value;
- green algal 96 h EC₅₀;
- fish chronic value;
- aquatic invertebrate chronic value; and
- algal chronic value.

Effective concentrations can either be measured or predicted. Regardless of the source of the effective concentration, the assessor must determine if each effect datum is valid, applicable to the chemical in question, and adequate for risk assessment. Measured toxicity data are preferred but predicted effective concentrations for a new chemical is a necessity when no measured toxicity data are available. So a Hazard Profile may consist of only measured toxicity data or only predicted toxicity data or any combination in between. Over 90% of the Hazard Profiles for new chemicals consist entirely of predicted effective concentrations.

When effective concentrations have to be predicted, Structure Activity Relationships (SAR) are used. SAR methods vary widely: from quantitative structure activity relationships (QSAR, Clements 1988), qualitative SARs, to selection of the best analog, for example, cationic dyes.

Concern Concentration

Once the hazard profile for the new chemical has been developed, a concern concentration (CC) has to be determined. A concentration of concern is that concentration of chemical which, if exceeded in the environment, may cause a significant risk. If the CC is not exceeded, it is assumed that the probability of a significant environmental risk occurring is too low to warrant regulatory action. The environmental CC is analogous to a reference dose (RfD) used in risk assessments for human health (Barnes and Dourson 1988, and USEPA 1991). Concern concentrations are calculated from the effective concentrations in the Hazard Profile by the use of assessment factors (USEPA 1984). Assessment factors (AsF) are similar to uncertainty factors (UF, Health Council 1989), and less similar to margins of safety (MOS) or margins of exposure (MOE, USEPA 1990). Four AsFs are used by OTS to set a CC for chronic risk: 1, 10, 100, and 1000. The selection of an AsF depends on the amount and type of toxicity data in the Hazard Profile; in general, the greater the amount of the data and the greater the quality of the toxicity data, the smaller the factor. For example, if the hazard profile contains the results of a field study and a chronic value is available for field observed effects of the chemical, then an assessment factor of 1 is used. An AsF of 1 has been used less than once a year in the new chemical program.

An assessment factor of 10 is used to calculate the CC for chronic risk when only toxicity data from laboratory studies are available, and the chronic value is known for the most sensitive species. The CC is calculated by dividing the lowest chronic value by 10. This AsF has been used frequently especially with new neutral organic chemicals (Auer et al. 1990).

A larger assessment factor of 100 is used only when extensive acute toxicity data are available. For example, the Hazard Profile contains data from the environmental base set, that is, fish acute value, aquatic invertebrate acute value, and green algal 96 h EC₅₀; or from five or more acute toxicity tests with only two groups of aquatic organisms (for example, fish and aquatic invertebrates; fish and algae; or aquatic invertebrates and algae). The concern concentration for chronic risk is calculated by dividing the lowest toxicity value (that is, EC₅₀ value) by 100. This has been the most frequently used AsF.

The largest assessment factor of a 1000 is used when the Hazard Profile contains the effective concentration from only one acute toxicity test. Such a Hazard Profile contains the greatest amount of uncertainty about the potential effects of a chemical. An AsF of 1000 is also occasionally used with chemicals that are suspected of having excess toxicity (Auer et al. 1990).

Concern concentrations for acute risk are also occasionally determined and are set by

dividing the acute no-effect-concentration (NEC) for fish or aquatic invertebrates or the algal chronic value by an UF of 10.

Exposure Assessment

The objective of the exposure assessment is to predict the environmental concentrations of a chemical from releases due to its production, processing, uses and disposal. Under TSCA, the great majority of chemical releases which result in release to the environment occur in streams and rivers. Releases of industrial chemicals to terrestrial ecosystems that can be quantified are rare. Most releases to the terrestrial environment are to landfills and deep well injections which generally do not result in releases to the surfaces of terrestrial ecosystems (Nabholz 1991).

The exposure assessment begins with the estimates of chemical release from the engineering report. The engineering report identifies all potential releases and estimates the amount of each release. Chemical release estimates are in terms of kilograms of chemical released per day from a site(s) for so many days per year. Experts in chemical fate determine what type of treatment the chemical is most likely to undergo after release from a site and before it reaches a stream. Generally, chemicals are subjected to some form of treatment in sewage processing plant (that is, publicly owned treatment works or POTW). The chemical fate expert will remove a percentage of chemical due to POTW treatment (that is, 0 to 99% removal) and predict the amount of chemical to be released to the environment after treatment as kg per day. The daily amount of chemical released after treatment (as kg per day) is instantaneously mixed with the daily amount of water in the stream (as L per day) to give a predicted environmental concentration (PEC) in $\mu\text{g per L}$ (ppb). After mixing with the stream, no losses are estimated after discharge and constant PECs are assumed, thus, resulting in a worst case exposure.

Under TSCA, two types of exposure assessments are done most frequently. In the first, which is called the Percentile Stream Flow Method and is done at FOCUS, 4 PECs are estimated for releases from multiple unknown sites, that is,

- PEC for the 50th percentile mean streamflow (50M),
- PEC for the 50th percentile low streamflow (50L),
- PEC for the 10th percentile mean streamflow (10M), and
- PEC for the 10th percentile low streamflow (10L).

For releases from known sites, only 2 PECs are estimated: one PEC for low flow and one PEC for mean flow.

Percentile streamflows for a particular stream—reach or for all stream—reaches receiving chemical releases from a particular type of chemical activity (for example, carpet fiber dyers) are derived from United States Geological Survey (USGS) data about streamflow in particular stream reaches. The low-flow streamflow is the 7Q10 streamflow, which is the lowest 7-day streamflow to occur over a 10 year period.

The second type of exposure assessment, which is called the Probability Dilution Model (PDM) Method (USEPA 1988), is done following FOCUS or during a Standard Review (SR). The assumptions about instantaneous mixing and no losses after discharge are still used, but in this method more information about streamflows and chemical release are used. This method predicts how many days per year the CC (or any other effective concentration) is exceeded using all the daily streamflows for the whole year, the amount of chemical being released per day after treatment, if any, and the estimated number of days of chemical release during the year.

Risk Assessment

Under Section 5 of TSCA, the quotient method is used, which simply compares the CC (or any effective concentration) to the PEC for the new chemical. If the PEC is greater than the CC, then there is a risk that the effect will be realized. At FOCUS, the lowest CC for chronic risk is compared to the PECs. Several scenarios are possible: (1) If the PEC is less than the CC, then the chemical is dropped from further review. (2) If the 10L and 10M PECs are greater than the CC, and the number release days to the environment are greater than 20, then a risk to the environment is expected and the chemical enters SR. (3) If only the 10L PEC is greater than the CC, but the 10M PEC is lower, then risk is estimated using the PDM Method: (3a) If the CC for fish and invertebrates is exceeded more than 20 days or the CC for algae is exceeded more than 4 days, then the chemical enters SR. The greater the number of days the CC is exceeded, the greater the risk. (3b) If the CC for fish and invertebrates is exceeded less than 20 days and the algal CC is exceeded less than 4 days, then the chemical is dropped from further review. (4) If the number of release days is less than 20, the lowest CC for acute risk is compared to the PECs. The possible scenarios for acute risk are homologous to those for chronic risk, except that the CC for acute risk to fish has to be exceeded only four days and the CC for acute risk to invertebrates has to be exceeded only two days for a finding of significant risk for acute effects. (5) For chemicals which have been subjected to a SR, the PDM Model is generally used to estimate environmental risk. For example, the PDM indicates how many days a CC or any effective concentration is exceeded. If the CC was derived from a 21-day ChV for aquatic invertebrates, then exceeding this CC receiving stream 250 days per year is a significant risk; exceeding this CC 25 days per year is a risk, but a low risk; and exceeding this CC only 5 days per year would indicate a very low probability of chronic risk to aquatic invertebrates. After SR, the PDM Model may be used to estimate risk at each release site(s) towards fish, aquatic invertebrates, and green algae in order to better quantify the type(s) of risk, the degree of risk, and the geographical extent of risk posed by a new chemical.

Case Studies

Neutral Organic Chemicals

Neutral organic chemicals are nonelectrolyte and nonreactive compounds, for example, solvents, that act like anesthetics or narcotics (Auer et al. 1990). Neutral organic chemicals include alcohols, ketones, ethers, alkyl halides, aryl halides, aromatic hydrocarbons, aliphatic hydrocarbons, sulfides, disulfides, and N-substituted anilines. These are the most frequently encountered compounds encountered under Section 5 and complete hazard profiles, that is, profiles with all 6 effective concentrations, are available for risk assessment. Compounds with molecular weights (MW) > 1000 and/or log octanol/water partition coefficients (K_{ow}) > 8 are generally assigned a low hazard concern because they are not expected to be toxic at saturation (that is, at their aqueous solubility limit) and are dropped at FOCUS. Compounds with $\log K_{ow}$ values of > 5 and < 8 are expected to be toxic only under chronic exposures and compounds with $\log K_{ow}$ values < 5 are expected to exhibit both acute and chronic toxicity. The geometric mean acute to chronic ratio (ACR) for these compounds averages about 10 for daphnids (Hermans et al. 1984) and fish (Broderius et al. 1989) when $\log K_{ow}$ values are < 5.

Organic Chemicals Showing Excess Toxicity

Organic chemicals with more specific mode(s) of toxic action other than narcosis (Auer et al. 1990) are more toxic than a neutral organic chemical with an equivalent K_{ow} and MW.

The amount of excess toxicity is related to K_{ow} , that is, as the K_{ow} decreases (or as the compounds become more water soluble) the amount of excess toxicity relative to the neutral organic chemicals increases. In other words, as the K_{ow} increases (or as the compounds become more water insoluble), the amount of excess toxicity decreases until, at some value of K_{ow} , the toxicity of the compound is not significantly different from the toxicity predicted using SARs for neutral organic chemicals or narcotic chemicals. The acrylates are a good example of this phenomenon (Clements 1988). The slope of the SAR for acrylates with respect to fish acute toxicity is smaller or shallower than the SAR for neutral organics (Note: this assumes that the logarithm of the fish acute value is regressed against the $\log K_{ow}$ value, so that as K_{ow} increases, the acute value decreases). The intercept of the regression equation for acrylates is, therefore, smaller than the intercept for neutral organics. The SAR for acrylates intercepts the SAR for neutral organics at a $\log K_{ow}$ of five.

Organic chemicals showing excess toxicity include acrylates, acrylamides, aldehydes, aliphatic amines, anilines, aziridines, benzotriazoles, carbamates, diazotiums, epoxides, esters, hydrazines, peroxy acids, phenols, propargyl alcohols, substituted ureas, sulfonamides, vinyl halides, α , β -diketones, benzyl halides, alkylsilanes, vinylsilanes, acid chlorides, sulfonyl chlorides, and many pesticides. Interception points between SARs for organic chemicals which have excess toxicity generally occur at about a $\log K_{ow}$ of five based on calculated K_{ow} values (Leo and Weinger 1985). However, there are some exceptions or chemical classes that have interception points at higher K_{ow} values. For example, the SAR for aldehydes intercepts the SAR for neutral organics at a $\log K_{ow}$ of 6 (Clements 1988), and anilines and phenols at a $\log K_{ow}$ of 7 (Veith and Brodenius 1987). This means that anilines will be acutely toxic to fish (as a fish 96 h LC_{50} value) up to a $\log K_{ow}$ value of 7.0. The acute toxicity of aliphatic amines is related to and is linear through a $\log K_{ow}$ of 7, however, beyond a $\log K_{ow}$ of 7.0, aliphatic amines are still acutely toxic to aquatic organisms. Acute toxicity data has been collected for aliphatic amines with $\log K_{ow}$ values as high as 22.0 (Platz and Nabolz 1990). Aliphatic amines exhibit acute toxicity through $\log K_{ow}$ values of 22.0 because they are self-dispersing and form micelles in water just as detergents do, thus, remaining bioavailable enough to cause acute toxicity. Acute toxicity for aliphatic amines with $\log K_{ow}$ values greater than 7.0 is predicted using the nearest analog method because toxicity is no longer related to K_{ow} .

Hazard profiles for organics with excess toxicity are generally incomplete. Profiles generally do not contain chronic values and many profiles only contain the fish acute value. The ACRs for these chemical classes are expected to be greater than 10 and are suspected of being related to $\log K_{ow}$, that is, as K_{ow} decreases, the ACR increases (or as K_{ow} increases, ACRs decrease). In other words, ACRs at low K_{ow} values are greater than 10, but decrease to 1 as K_{ow} values increase to 8 or greater. Metabolism may modify these expectations. For example, acrylamide is known to have large ACRs and is not metabolized rapidly, however, acrylates are known to be metabolized rapidly, and acute and chronic toxicity data for hydroxyethyl acrylate (Russum 1989a, 1989b) suggest that the ACRs for acrylates may be less than 5.

Surfactants

Surfactants with MWs <1000 are considered to be primarily surface active agents, that is, chemicals that damage respiratory membranes, during acute exposures, but systemic toxicants during chronic exposures because they can be absorbed through respiratory membranes. Surfactants with MWs >1000 are considered to be only surface active agents since they are too large to be absorbed. Surfactants are divided into four classes: anionic

(negatively charged), nonionic (neutral or no charge), cationic (positively charged), and amphoteric (negative and positive charges). All surfactants are assumed to have parabolic structure-activity relationships, that is, fish acute toxicity is related to the size of the hydrophobic component in a parabolic manner when the size of the hydrophilic component remains constant. When the hydrophobic component is small relative to the hydrophilic component, toxicity is low; when the components are nearly balanced, toxicity is maximized; and when the hydrophobic component becomes larger than the hydrophilic component, toxicity decreases.

Anionic Surfactants—The three most frequently encountered anionic surfactants in the new chemical program are sulfonates, phosphonates, and fatty acids. The strongest surfactants are the sulfonates and the weakest are the fatty acids. The easiest to assess are the sulfonates because of the large amount of information for linear alkyl benzene sulfonates (LAS) concerning their acute and chronic toxicity (Clements 1988) to fish and aquatic invertebrates. The amount of toxicity information for anionic surfactants towards green algae is relatively very small. The most difficult anionic surfactants to assess are the phosphates because they generally exist as mixtures of mono and dialkylphosphates, the amounts of mono and dialkyl moieties can vary greatly, and development of reliable SARs are difficult because of this variability in structure and composition. As a result, hazard assessment involves searching for the nearest analog(s) from the OTS PMN ECOTOX Data Base (Nabolz 1990). The assessment of fatty acids was greatly improved with the publication of several SARs by Onitsuka et al. (1989). Hybrid surfactants, for example, an LAS with ethoxylates between the alkyl group and the benzene ring or an LAS with a carboxylic acid near the sulfonate, are assessed by combining knowledge about the various classes of surfactants. For example, information about how ethoxylate groups decrease the toxicity of alcohol ethoxylates is used to reduce the toxicity of an ethoxylated-LAS and it is known (Nabolz 1990) that if you add a carboxylate near the sulfonate of a alkylsulfonate surfactant, the fish acute toxicity of the alkylsulfonate is increased about 10 times. The ACR for all anionic surfactants is predicted to be about 6.5 based on data for the LAS surfactants (Clements 1988).

Nonionic Surfactants—The most frequently assessed nonionic surfactants are the alcohol ethoxylates. A large amount of information concerning their acute toxicity towards fish and aquatic invertebrates has been synthesized by Clements (1988). As was observed for the anionic surfactants, the amount of toxicity information for green algae is relatively very small. The ACR for the nonionic surfactants is assumed to be about 10 based on data for neutral organic chemicals and the expectation that they will be absorbed more rapidly and excreted more slowly from aquatic organisms relative to the anionic surfactants.

Cationic Surfactants—The most frequently encountered type of cationic surfactants in the new chemical program is the quaternary ammonium compounds. Phosphoniums and sulfoniums are rare. Cationic surfactants are considered the most toxic class of surfactants (Clements 1988). Algae are assumed to be the most sensitive species during acute exposures, and fish and aquatic invertebrates more sensitive during chronic exposures. The ACR used for the cationic surfactants is assumed to be equal to or greater than 10. When new cationic surfactants are expected to pose a significant risk to the environment, five toxicity tests are recommended: the fish acute toxicity test with clean dilution water, that is, total organic carbon (TOC) concentrations <2.0 mg/L, the daphnid acute toxicity test in clean dilution water, the algal toxicity test, the fish acute toxicity with 10 mg humic acid (HA) per L added to dilution water, and the fish acute toxicity test with 20 mg HA per L added to the dilution water. All tests are done under static conditions and nominal concentrations based on 100% active ingredients (AI) of cationic surfactant. In addition, the concentration of total organic carbon (TOC) is measured in the controls of all toxicity

tests. When the test data are analyzed, the three fish 96 h LC₅₀ values are regressed against TOC. The fish 96 h LC₅₀ value in the presence of 10 mg TOC/L is predicted and divided by the fish 96 h LC₅₀ value in clean dilution water. The difference between these LC₅₀ values is the mitigation factor (MF) for 10 mg TOC/L. The MF for cationic surfactants is expected to be less than 20. All of the effective concentrations in the hazard profile that are based on intrinsic toxicity in clean water are multiplied by this MF. The hazard profile expected in the presence of 10 mg TOC/L is then used in risk assessment. For example, if the MF for a cationic surfactant in the presence of 10 mg TOC/L is 24, then the CC for the cationic surfactant in clean water, that is, TOC is less than 2.0 mg/L, is multiplied by 24. If the CC in clear dilution water was 0.004 mg/L, then the CC in the presence of 10 mg TOC/L will be 0.100 mg/L. If the risk to aquatic organisms living in the water column is not mitigated by the presence of dissolved organic carbon (DOC) in the water column, then chronic toxicity testing is recommended with fish and aquatic invertebrates in clean dilution water. If the risk to water column is mitigated, then toxicity testing with benthic organisms or organisms which are known to ingest sediments, for example, tadpoles, is recommended. Toxicity mitigation testing is recommended because it is known that DOC binds with cationic chemicals; neutralizes the positive charges, makes the cationic chemical less toxic, and makes the cationic chemical less bioavailable (Cary et al. 1987). Humic acid was selected as the representative dissolved organic carbon (DOC) based on research done by Cary et al. (1987) and further analysis done by (Nabholz and Zeeman 1991). Mitigation factors based on 10 mg TOC/L are used in hazard and risk assessments for three reasons: (1) concentrations of humic acid in natural waters are rarely known for specific sites, (2) the average measured amount of TOC in natural freshwater of the US is about 6.79 mg TOC/L (Lynch 1987, Nabholz and Zeeman 1991), and (3) 10 mg TOC/L is a round number close to 7 which errs on the side of safety.

Amphoteric Surfactants—These surfactants are assessed depending upon the dominant charge of the surfactant. If the cationic charge is dominant, for example, ethoxylated quaternary ammonium surfactants, then the surfactant is assessed as a cationic surfactant. If the cationic charge is weak, for example, ethoxylated β-amine surfactants [ETHOMEEN], then the surfactant is assessed as a nonionic surfactant (Clements 1988). Ethoxylated fatty acids and ethoxylated sulfonates are assessed as anionic surfactants. Surfactants consisting of an amine and a carboxylic acid are assessed as an anionic surfactant.

Polymers—Polymers are divided into four classes depending on the type of electronic charge of the polymer: nonionic (neutral); anionic (negative charge); cationic (positive charge); and amphoteric (mixture of positive and negative charges on same molecule) polymers.

Polymers which have number average molecular weights (M_{Wn}) <1000 and which are water soluble or dispersible may be of concern because of their potential (1) to be toxicologically similar to polymers whose M_{Wn} >1000 and (2) to be absorbed through biological membranes and cause systemic effects. Polymers with M_{Wn} <1000 are generally assessed as a monomer is assessed, that is, based on the type of functional group(s) in the compound.

Polymers which have M_{Wn} >1000 and that are water soluble (or self-dispersing) are not expected to be absorbed through biological membranes, and are expected to assert their toxicity by affecting the outer membranes of aquatic organisms or the near environment of the organism (for example, overchelation of nutrient elements). Insoluble polymers are not expected to be toxic unless they are ground up into fine particles. The toxicity of finely ground particles is due to indirect (physical) toxicity (for example, the clogging of respiratory organs such as gills) and only occurs at high concentrations, that is, acute

toxicity values of greater than 1000 mg/L and chronic toxicity values of greater than 50 mg/L. The toxicity of finely ground insoluble polymers does not depend upon the chemical structure of the polymer.

Anionic Polymers—Polyanionic polymers that have M_{Wn} >1000 and which are water soluble (miscible or self-dispersing) are of concern for aquatic toxicity. Polyanionic polymers are divided into three subclasses: (1) poly(carboxylic acids), (2) polyaromatic sulfonates), and (3) poly(aliphatic sulfonates).

(1) Poly(carboxylic acids) are of concern only for their toxicity to green algae. Toxicity to algae as defined by the 96 h EC₅₀ for growth inhibition, is moderate with toxicity values ranging from 1 to 100 mg/L (ppm). It appears that the mode of toxic action of these poly(carboxylic acids) is overchelation of nutrient elements needed by algae for growth. When enough calcium (as divalent cation) is added to a polymer to satisfy its anionic charges, toxicity to algae is mitigated. It is known that calcium (as calcium carbonate in water with hardness of 100 to 150 mg/L as CaCO₃) added to algal growth medium will also mitigate toxicity to an equal degree.

Poly(acrylic acid) is moderately toxic to green algae (Nabholz 1990) and appears to be the most potent form of poly(carboxylic acid) in its ability to chelate nutrient elements. Its chemical structure is —[C(COOH)]— where you have a carboxylic acid on every other (or alternating) carbon(s) in the polymer backbone. The carboxylic acids are paired and equal distance from the polymer backbone. Test data for poly(maleic acid) from Nabholz (1990) indicated low toxicity to algae, that is, 96 h EC₅₀ = 560.0 mg/L, and, thus, a weak ability to chelate nutrient elements. In this polymer, there is a carboxylic acid on every carbon of the polymer backbone, that is, —[C(COOH)C(COOH)]—. Additional PMN test data (Nabholz 1990) have suggested that (1) when the carboxylic acids are further separated, for example, a carboxylic acid on every fifth carbon of the polymer backbone, or (2) when the carboxylic acids are different distances from the polymer backbone, the polymer's ability to chelate nutrient elements is reduced. The test data to support these last two conclusions are weak. In summary, the most potent structure for poly(carboxylic acid) polymers is paired acids which are equal distant from the polymer backbone and which have one acid on alternating carbons.

The toxicity of poly(acrylic acid) polymers has been shown to be mitigated 13 times by the addition of one equivalent of Ca⁺⁺ to the polymer before testing (Nabholz 1990). PMN test data have indicated that the 96 h EC₅₀ increased from 37.4 mg/L to 500 mg/L if you chelate the polymer with divalent ions before exposure to algae. This indirect toxicity to algae via overchelation of nutrient elements may be a laboratory artifact because (1) many poly(carboxylic acid) polymers are used as scale inhibitors and are released to the natural environment, chelated with Ca and Mg. (2) these polymers are initially tested as the Na or K salt, and (3) the OTS Environmental Test Guideline recommends a growth medium which has a hardness of only about 15.0 mg/L as CaCO₃. This represents very soft water and the average hardness of freshwater in the United States is about 120.0 mg/L. In those cases where the polymer is not used as a scale inhibitor and is released to the environment as the Na or K salt, the hardness of the receiving waters (that is, 120.0 to 150.0 mg/L) may cause a substantial mitigation of the toxicity relative to the toxicity observed in the standard algal toxicity test. There are now sufficient test data to demonstrate the amount of mitigation due to moderately hard growth medium.

Polymers used as scale inhibitors and released to the environment chelated with calcium and magnesium ions should be tested three times with freshwater green algae: (a) test chemical as is, (b) test chemical with an equivalent of Ca⁺⁺ added to the stock solution, and (c) test chemical as is but tested with modified algal test/growth medium. Calcium alone or Ca and Mg is added to attain a measured hardness of about 150 mg/L as CaCO₃. If

Ca and Mg are added together, then add Ca and Mg in the ratio of 2 Ca to every Mg. Test results from the test with an equivalent of Ca added to the polymers will be used to assess releases from use. Test results with the polymer as the Na or K salt will be used to assess releases from manufacturing and processing. All stock solutions should be adjusted to pH 7 before testing because PMN test data have shown that, if the polymer is tested as the acid or with excess acid, the toxicity from the acid was greater than the toxicity of the polymer via overchelation.

Polymers not used as scale inhibitors and are released to the environment as produced (generally as the Na and K salts) should be tested twice with green algae: (a) the polymer as is, and (b) the polymer with modified algal test/growth medium.

(2) Poly(aromatic sulfonates). Some poly(aromatic sulfonate) polymers with MWn greater than 1000 may be of moderate concern for acute toxicity towards fish and green algae. Polymers in this class which have shown toxicity have the following characteristic monomers: sulfonated phenols, sulfonated cresols, sulfonated diphenylsulfones, sulfonated diphenyloxides, and sulfonated diphenylsulfones. This concern is based on two facts. The first is test data for 8 PMN polymers (Nabholz 1990) which indicated acute toxicity values of about 5.0 mg/L for fish (as a 96 h LC₅₀) and 20.0 mg/L for algae (as a 96 h EC₅₀). This evidence is weak because while these polymers have MWn's equal to or greater than 1000, they had substantial amounts of low molecular weight (LMW) components: >10% <500 and >25% <1000. The observed toxicity could have been due to the LMW components. However, the second fact is that the Agency has recently received data for a PMN polymer (Nabholz 1990) which had a MWn = 12 200, <0.1% <500, and <0.1% <1000, contained a carboxylic acid substituted diphenylsulfone, and was moderately toxic to aquatic organisms, that is, fish 96 h LC₅₀ = 72.0 mg/L, daphnid 48 h LC₅₀ = 86.0 mg/L, and green algal 96 h EC₅₀ = 40.0 mg/L (hardness [H] of medium = 18.0 mg/L as CaCO₃). This polymer was tested three additional times with harder growth medium. There was no significant mitigation of the toxicity, that is, H = 46 mg/L, EC₅₀ = 24.0 mg/L, H = 152 mg/L, EC₅₀ = 20 mg/L, and H = 160 mg/L, EC₅₀ = 47.0 mg/L. The only common monomer between these two sets of polymers was the acid substituted diphenylsulfone.

Poly(aromatic sulfonate) polymers that have been shown to have low toxicity (that is, acute toxicity values greater than 100.0 mg/L) or are highly suspected of having low toxicity are composed of the following monomers: benzene sulfonates and sulfonated naphthalene.

(3) Poly(aliphatic sulfonates). There are not enough test data for these polymers to draw any firm conclusions about their toxicity. However, it is suspected that if these polymers show toxicity to aquatic organisms it will be to algae as was observed for the poly(carboxylic acid) polymers.

Nonionic Polymers—Polynonionic polymers which have MW > 1000 are of low concern.

Cationic Polymers—Polycationic polymers include polyamines (primary amines, secondary amines, and tertiary amines); quaternary amines; polysulfoniums; and polyphosphoniums. Polymers of concern have MV_n's > 1000 and are water soluble (miscible or self-dispersing). Polymers based on polyglucosamines (that is, chitosan) are much less toxic (Nabholz 1990) than predicted and are no longer of concern.

Aquatic toxicity in clean water (that is, TOC < 2 mg/L) increases exponentially with increasing cationic charge density, that is, protonated and/or quaternized-N, S or P. An SAR for polycationic polymers has been published by Clements (1988). Green algae are about six times more sensitive than fish (that is, algal 96 h EC₅₀ versus fish 96 h LC₅₀). The mode of toxic action for these polymers is surface active (that is, they react with biological

membranes), however, when MW falls below 1000, some systemic toxicity may also occur.

The aquatic toxicity of these polymers with MWn > 1000, <10% <500, and <25% <1000 is highly mitigated by the presence of dissolved organic carbon (DOC) in water. For polymers with charge densities = >2.4 cations/1000 MWn (or equivalent weight <400 or >3.3% amine-nitrogen), the acute toxicity to fish is reduced about 94 times (Nabholz 1990, Nabholz and Zeeman 1991) when the measured TOC in water is 10 mg/L as the result of adding humic acid to dilution water (that is, TOC = 10 mg/L is equivalent to 27.6 mg/L humic acid, sodium salt; CASRN [1415-93-6]; Aldrich H1,673-2; Merck Index 10,4649). This mitigation factor of 94 is based on the results of testing 8 polymers.

The toxicity of polymers with MWn > 1000 and significant amounts of LMW material (that is, >10% <500 and >25% <1000) is mitigated less by dissolved organic matter in the water column (Nabholz 1990). Two polymers with significant amounts of LMW material (that is, one with MWn = 1000, 23.3% <500, and 32.3% <1000; and another with MWn = 1030, 12% <500, and 38% <1000) had mitigation factors of only 26 and 21, respectively.

The aquatic toxicity of polymers with charge densities = >2.4 cations/1000 MWn (or equivalent weights <400 or >3.3% amine-nitrogen) are now of low concern for aquatic organisms living in the water column of the aquatic environment because of the predicted low risk.

There is one known exception to the mitigation/low bioavailability scenario for these polymers. When these polymers are formulated with excess acid, for example, 20% excess acid more than you need to protonate all of the amines in a polymer; and the product pH is about 2, these polymers will fail to flocculate DOC in the water column and DOC does not appear to mitigate the acute toxicity to fish.

Many polycationic polymers are designed to react with DOC in the water column to form an insoluble flocculent. This flocculent eventually settles on sediments and accumulates in sediment. Sediment toxicity testing with species which ingest sediment has shown that polycationic polymers with charge densities of = >3.0 cations/1000 MWn (or = >4.2% amine-nitrogen or an equivalent weight = <333.0) are not bioavailable to cause any toxicity and are thus of low concern in sediments (Rogers and Whit 1989).

The testing scheme for cationic polymers is identical to the scheme for cationic surfactants.

Amphoteric Polymers—Polyamphoteric polymers with equal numbers of cationic charges and anionic charges or with greater cations than anions are treated as a polycationic polymer. The toxicity of the polycationic polymer portion of the polymer is reduced based on the number of anionic charges. When there are greater numbers of anions than cations, the polymer is treated as a polyanionic polymer.

Dyes—Organic dyes are divided into four classes depending on the type of electronic charge of the dye: nonionic (neutral dyes); anionic (negative charge or acid dyes); cationic (positive charge) dyes; and amphoteric (mixture of positive and negative charges on same molecule) dyes.

Acid Dyes—Analysis of over 200 acid dyes (Auer et al. 1990, Nabholz 1990, Sigman et al. 1983, Tonogai et al. 1979, Little and Lamb 1972, ADM 1974) have indicated that some monoacid and diacid dyes can show moderate to high toxicity (that is, acute values <100 mg/L and <1 mg/L) to fish and aquatic organisms. Dyes with three or more acid groups showed low toxicity (that is, acute values >100 mg/L) towards fish and invertebrates. All acid dyes showed moderate toxicity towards green algae. Analysis of available data (Auer et al. 1990, Nabholz 1990) has suggested that effects to algae were not the result of direct toxicity but represented an indirect effect due to shading. Senior regulatory decision-makers in OTS decided in 1988 that the risk to algae from indirect (shading)

toxicity was not an unreasonable risk for two main reasons: (1) algae grew quickly as soon as the dye was diluted, and (2) the release of colored effluents in the U.S. generally results in immediate complaints by citizens to their local authorities, for example, county and state governments. The rapid response by the public generally results in quick regulatory action by local officials.

Since there is no SAR for acid dyes (Auer et al. 1990), hazard profiles for monoacid dyes are developed using measured data or data for the nearest analog(s). Testing recommendations consist of acute toxicity tests with fish and invertebrates.

Neutral Dyes—Neutral dyes are assessed as neutral organic chemicals are assessed.

Cationic Dyes—Cationic dyes are assessed as cationic surfactants and polymers are assessed. Since there is no SAR for cationic dyes (Auer et al. 1990), hazard profiles are developed using measured data or data for the nearest analog(s). All of the available toxicity information for cationic dyes has been collected and grouped by similarity of structure within several broad categories, that is, dyes with delocalized charge, dyes with four localized charges, dyes with three localized charges, etc. (Platz et al. 1988). The ACR for one cationic dye with delocalized charge has been measured in daphnids and was 15 (Nabholz 1990).

Testing recommendations vary based on the type of dye: Dyes with delocalized cationic charge and dyes with one or two localized cations—the base set of toxicity tests in clean dilution water are recommended. Mitigation testing with HA does not need to be done because test data have shown only weak mitigation of toxicity in the presence of 10 mg TOCL. Test data for three dyes with delocalized charge and one dye with two localized charges (Nabholz 1990) have shown mitigation factors of 3.4 and 7.1, respectively, in the presence of 10 mg TOCL; and

Dyes with three or more localized cations—The base set of toxicity tests and two fish acute toxicity tests with HA are recommended. No test data for these dyes have been evaluated. It is expected that the mitigation factors will be equal to or greater than 7.0 but less than 20.0.

Amphoteric Dyes—Amphoteric dyes with equal numbers of cationic charges and anionic charges or more anionic charges than cationic charges have been shown to exhibit low toxicity towards fish and aquatic invertebrates (Nabholz 1990) and are assessed as an anionic dye would be assessed. Those dyes with a greater number of cations than anions are treated as a cationic dye.

Polyanionic Monomers

Polyanionic monomers, for example, ethylenediaminetetraacetic acid (EDTA), are of concern only for their toxicity to green algae. Toxicity to algae is moderate (Nabholz 1990) and it appears that the mode of toxic action of these polyanionic monomers is overchelation of nutrient elements needed by algae for growth. Polyanionic monomers are assessed similarly to the poly(carboxylic acid) polymers.

Compounds That Hydrolyze/React and Polymerize

Compounds that fit this assessment category are alkylloxysilanes and isocyanates. They are reactive organic chemicals which tend to polymerize when they hydrolyze. The tendency to polymerize increases as the concentration of compound increases in water. The alkylloxysilanes have been shown to have high toxicity towards algae, moderate toxicity towards daphnids, and low toxicity towards fish (Nabholz 1990). There is little toxicity data for the isocyanates but moderate toxicity towards fish has been observed

(Verschuereen 1983). These toxicity test results have been the result of toxicity tests using the static method and nominal concentrations. There is uncertainty about what form of the chemical is causing the toxicity: parent material that has not yet hydrolyzed or the hydrolysis product(s). Because of this uncertainty, it is recommended that chemicals of this type be tested twice using the environmental base set of tests. (1) In the first test, no stock solution is prepared. The compounds are slowly added to the test chambers by direct dilution while the dilution water is stirred. The organisms are added within 10 min of adding the chemical. The static renewal method with 24 h renewals is used for daphnids and fish, and the static method is used with green algae. Nominal concentrations based on 100% AI are used for all tests. (2) In the second test, a stock solution is made by adding water to a volumetric flask first, adding the chemical slowly while the water in the flask is stirred. After the chemical is completely added, fill the flask with water and, while stirring, let stand until all of the chemical has hydrolyzed, that is, at least, 6 half-lives. Adjust the pH of this stock solution to 7 before testing. The static method with nominal concentrations can be used for all tests. The results of these two sets of tests will allow the assessor to determine the source of the toxicity and to perform a more rigorous hazard and risk assessment.

Compounds That Hydrolyze/React and Do Not Polymerize

Compounds that fit this assessment category are acid chlorides, sulfonyl chlorides, and peroxy acids. Acid chlorides (Nabholz 1990) and sulfonyl chlorides (Verschuereen 1983) are moderately toxic towards fish and peroxy acids are highly toxic towards fish with acute toxicity values of about 0.300 mg/L (Nabholz 1990). The uncertainties for this group of compounds are similar to the uncertainties discussed above for the reactive compounds which tend to hydrolyze. Therefore, the recommended testing is the same except for the cautions about adding the chemical to dilution water in such a way as to minimize polymerization.

Metals—Metals are divided into two groups: inorganic metal forms and organometallic forms.

Inorganic Metals—Some metals have a large amount of toxicity information, for example, copper and silver, while other metals have very little to no information, for example, bismuth and rhodium. Assessments of metals with a substantial amount of information may contain high amounts of uncertainty because the form of the metal is the oxide or the sulfide while all of the toxicity information is on the chloride salt. There are no SARs for metals and the basis for potential SARs is very inadequate. Development of hazard profiles is dependent on nearest analog(s) techniques, for example, metals belonging to the same family on the periodic table of elements. Recommended testing consists of the base set of toxicity tests and two additional fish acute toxicity tests with humic acid added to dilution water when the metal to be tested is a cationic form and just the base set when the form is neutral or anionic.

Organometallics—There is very little information about organometallics outside of data for organotins, organomercurys, and organoarsenics. In general, there is more concern for the organometallic form of a metal than for the inorganic forms because the organometallic is assumed to be more easily taken up by aquatic organisms and to be more highly bioconcentrated. Toxicity data for organometallics is subject to SAR development since the potential of the organic portion of the organometallic to bioconcentrate in aquatic organisms can be estimated. A series of SARs for organotins have been published by Vighi and Calamari (1985). Recommended testing is the environmental base set of tests.

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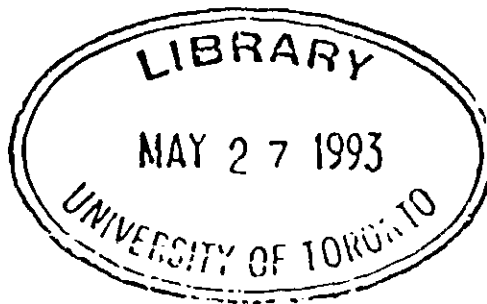
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Foreword

The First Symposium on Environmental Toxicology and Risk Assessment was held 14–16 April 1991 in Atlantic City, New Jersey. ASTM Committee E-47 on Biological Effects and Environmental Fate sponsored the symposium. Wayne G. Landis (Western Washington University), Jane S. Hughes (Malcolm Pirnie, Inc.), and Michael A. Lewis (Battelle Columbus Laboratories) were the symposium chairmen. They also served as editors of this publication.

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Peer Review Policy

Each paper published in this volume was evaluated by three peer reviewers. The authors addressed all of the reviewers' comments to the satisfaction of both the technical editor(s) and the ASTM Committee on Publications.

The quality of the papers in this publication reflects not only the obvious efforts of the authors and the technical editor(s), but also the work of these peer reviewers. The ASTM Committee on Publications acknowledges with appreciation their dedication and contribution to time and effort on behalf of ASTM.

STP 1179

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Risk Assessment*

*Wayne G. Landis, Jane S. Hughes, and
Michael A. Lewis, Editors*

ASTM Publication Code Number (PCN)
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1916 Race Street
Philadelphia, PA 19103

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Environmental & Toxicology & Risk Assessment

Landis/Hughes/Lewis
editor

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14

**PHARMACEUTICAL
MANUFACTURERS ASSOCIATION**

**INTERIM GUIDANCE
TO THE
PHAMACEUTICAL INDUSTRY
FOR
ENVIRONMENTAL ASSESSMENT
COMPLIANCE
REQUIREMENTS
FOR THE
FDA**

v 7
July, 1991

FDA Corres



NDA 20-193

Food and Drug Administration
Rockville MD 20857

Baker Norton Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404

JUN 13 1996

Attention: Ed Mitchell, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Mitchell:

We acknowledge receipt on April 11, 1996, of your April 10, 1996, amendment to your new drug application (NDA) for Elmiron (pentosan polysulfate sodium) 100 mg capsules.

This amendment contains additional clinical information submitted in response to our March 1, 1996, approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is October 8, 1996.

Should you have any questions, please contact Mrs. Susan Cusack, Consumer Safety Officer, at (301) 443-1560.

Sincerely yours,

Patricia Y. Love, M.D., M.B.A.
Director, Division of Medical Imaging
and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Cusack

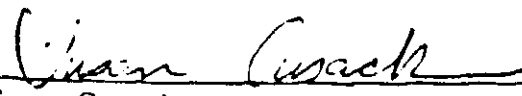
RECORD OF TELEPHONE CONVERSATION/MEETING	Date: January 23, 1996
Dr. Paserchia requested the following additional information:	NDA/IND#: 20-193
1. On page 33 of the June 1995 Investigator's brochure there are 3 serious adverse events described as: Weakness, progressing to death. Hemoptysis, and Hemiplegia. Please supply the case report forms for these patients. 2. In appendix F of the June 1995 Investigator's brochure, there are 5 deaths reported. Please supply the case report forms for these patients. 3. Also in appendix F there are 2 serious adverse events described as: Diarrhea and Dehydration; and Abdominal Pain. Please supply the case report forms for these patients. 4. Was the to-be-marketed formula the only formulation used during the compassionate use program?	Telecon/Meeting initiated by: ☐ Applicant/Sponsor ☒ FDA By: Telephone Product Name: Elmiron Firm Name: Baker-Norton Name and Title of Person with whom conversation was held: Steve Viti Phone: 305-590-2444
<i>Susan Cusack</i> 1-24-96	
Susan Cusack Consumer Safety Officer	
cc: NDA 20-193 HFD-160 Division File HFD-160 Cusack/Paserchia file name: 20193ja2.3tc	



The information has just arrived and is being processed. The document number is 20193ja2.3tc

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RECORD OF TELEPHONE CONVERSATION/MEETING	Date: December 8, 1995
Dr. Paserchia requested that the following questions be conveyed to the sponsor: 1. In the case report form for the Compassionate Use study (page 100039, Volume 10.2, dated August 31, 1995), the form for reporting adverse experiences clearly asks for the severity of the ADR. Yet in the "Maximum Severity" column of the database, most ADR's have at least 50% of the severity score reported as "Unknown". Please explain this finding. 2. Also, the database reports the number and percentage of patients who experienced each particular ADR during the Compassionate Use study. Please report the number and percentage of patients who experienced each particular ADR during: a. weeks 0 thru 4 b. weeks 5 thru 8 c. weeks 9 thru 12 d. a cumulative for the first 3 months e. a cumulative for the first 6 months f. a cumulative for the first 12 months I asked the Steve to submit items a-d ASAP. I also told him that item e was a high priority but that item f was a lower priority for now. <i>Susan Cusack Dec 8 1995</i> Susan Cusack Consumer Safety Officer cc: NDA 20-193 HFD-160 Division File HFD-160 Cusack/Paserchia file name: 20193dec.8tc	NDA/IND#: 20-193 Telecon/Meeting initiated by: ☐ Applicant/Sponsor ☒ FDA By: Telephone Product Name: Elmiron Firm Name: Baker-Norton Name and Title of Person with whom conversation was held: Steve Viti Phone: 305-590-2444 <i>This information was submitted 12-11-95 X Cusack</i>

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: November 30, 1995
Ms. Slade called on November 29 to inquire about and discuss the approval status of Elmiron. I called Steve Viti of Baker Norton to request a copy of the letter submitted to the Office of Orphan Products Development, which authorizes the FDA to discuss Elmiron with Ms. Slade. He faxed the letter, and at my suggestion, submitted a copy of it to the NDA. Dr. Love returned Ms. Slade's call and informed her that the company submitted an amendment to their application in August. This review is progressing and we expect to take an action on this NDA by the user fee goal date in February. Ms. Slade expressed her concerns that the approval process has taken a very long time. Dr. Love reiterated that the review is underway, the submission is not "sitting on a shelf". She briefly described the levels of review that are required. She also emphasized that we are actively involving the company when appropriate to ensure that we have everything necessary to complete the review. Finally, she stated again that we expect to take an action by the goal date.  _____ Susan Cusack Consumer Safety Officer cc: Original NDA HFD-160 Div File HFD-160 Cusack/Love file name: 20193ica.tc	NDA#: 20-193 Telecon/Meeting initiated by: ☐ Applicant/Sponsor ☒ FDA By: Telephone Product Name: Elmiron Firm Name: Baker Norton Name and Title of Person with whom conversation was held: Ms. Debra Slade, President, Interstitial Cystitis Association Phone: 914-923-1916

Cusack

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: October 23, 1995
At the request of the Medical and Statistical reviewers, I called Baker Norton to determine if they had submitted any revised draft labeling, since the original NDA submission. Steve Viti informed me that their February 11, 1994 submission contained draft labeling. He also stated that they realize that the labeling needs further revision and are anxious to discuss this with us. I stated that as the review progressed, if the application was otherwise approvable, we would discuss and labeling revisions that are necessary. For ease of reference, Mr. Viti faxed me a copy of the labeling that was submitted on February 11, 1994. <i>Susan Cusack Oct 25, 1995</i> Susan Cusack Consumer Safety Officer cc: Original NDA 20-193 HFD-160 Division File HFD-160 Cusack file name: 20193tc.O23	NDA#: 20-193 Telecon/Meeting initiated by: ☐ Applicant/Sponsor ☒ FDA By: Telephone Product Name: Elmiron Firm Name: Baker Norton Pharmaceuticals Name and Title of Person with whom conversation was held: Steve Viti, Regulatory Affairs Phone: 305-590-2444



Cusack

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: October 12, 1995
I called Mr. Viti to verify his fax number and inform him that the chemistry review of the amendment submitted on 5/22/95 was complete and that I would fax him the reviewer's draft comments. <i>Susan Cusack Oct 12, 1995</i> Susan Cusack Consumer Safety Officer cc: Original NDA 20-193 HFD-160 Division File HFD-160 Cusack file name: 20193tc.O12	NDA#: 20-193 Telecon/Meeting initiated by: ☐ Applicant/Sponsor ☒ FDA By: Telephone Product Name: Elmiron Firm Name: Baker Norton Pharmaceuticals Name and Title of Person with whom conversation was held: Steve Viti, Regulatory Affairs Phone: 305-590-2444



**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
September 21, 1995

I called Mr. Viti and informed him that the date on our acknowledgement letter of their 8-31-95 major amendment should have been September 19, 1995, not 1994.

Mr. Viti said he'll cross out 1994 and correct it to 1995.

cc: OrigNDA
HFD-160/DivFile

NDA/IND#:
NDA 20-193

**Telecon/Meeting
initiated by:**

Applicant/Sponsor

FDA

By: Telephone

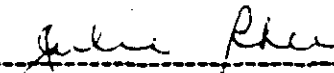
Product Name:
Elmiron

Firm Name:
Baker Norton
Pharmaceuticals, Inc.

**Name and Title of Person
with whom conversation
was held:**

Mr. Steve Viti
Regulatory Affairs

Phone:
(305) 590-2444



Name: Julie Rhee

DIV-

NDA 20-193

SEP 19 1995

Baker Norton Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404

Attention: Ed Mitchell, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Mitchell:

We acknowledge receipt of your August 31, 1995, amendment to your new drug application for Elmiron Capsules, 100 mg.

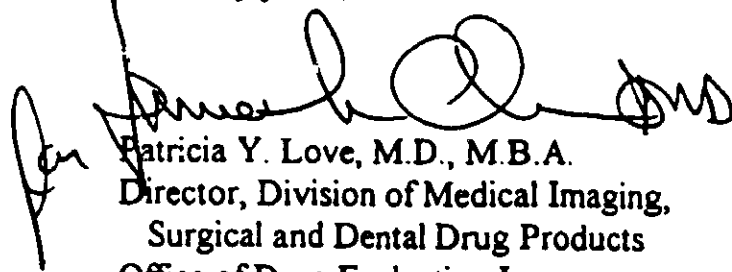
The amendment contains additional information submitted in response to our October 28, 1994, approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the new due date is February 28, 1996.

Should you have any questions, please contact:

Mr. Stephen McCort
Consumer Safety Officer
(301) 443-1560

Sincerely yours,



Patricia Y. Love, M.D., M.B.A.
Director, Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

9/18/95

cc:

Orig. NDA 20-193

HFD-160/Div. Files

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R/D by: AChapman-09-14-95 cso\n20-193.ack

ACKNOWLEDGEMENT

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NDA 20-193

JUN 29 1995

Baker Norton Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404

Attention: Ed Mitchell, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Mitchell:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Elmiron (pentosan polysulfate sodium).

We also refer to the meeting between representatives of your firm and Agency staff on February 16, 1995, and your meeting minutes dated March 2, 1995.

Upon review of the minutes, there are several areas where our minutes differ or where clarifications or comments are needed. The areas of most significant discrepancy are discussed according to the sections in your minutes:

REGARDING THE SUMMARY SECTION, Page 2

- 1st Point: While we are sensitive to the need for additional treatment for Interstitial Cystitis, there was not common agreement between Baker Norton Pharmaceuticals, Inc. (BNP) and the Agency that Elmiron provides substantial benefit for a subset of Interstitial Cystitis (IC) patients. An approval decision must be data driven. As stated in our non-approval letter of October 28, 1994, more data are needed.
- 2nd Point: We agreed that efficacy of a drug in IC could be evaluated by subjective endpoints. One such endpoint is a global improvement score.

3rd Point: We restated our concern that the inclusion of data from investigators common to studies E001 and E002 reduces our confidence in the independent outcomes of the two studies. We restated our position that study E002 could be considered one of the needed two adequate and well-controlled pivotal trials to support approval of the drug. In addition to study E002, a second adequate and well-controlled trial is still needed.

4th Point: Regarding what is needed for the second trial, our best recommendation was for the completion of a new study. It was agreed, however, that data from the compassionate use program could be reexamined to determine its ability to stand as the second adequate and well-controlled trial. The data submitted in July, 1993 was considered for safety only. This open label use study was not designed in manner to provide substantive benefit information; hence, it was not part of the efficacy database for the approval/not-approval decision. Studies E001 and E002 were the controlled clinical trials that were submitted in the July 13, 1993 submission; and these were the basis for the Agency's decision.

Given your meeting discussion of the manner in which the open label data were collected, the compassionate use experience might be able to provide sufficient additional efficacy data. In order to do so we suggested the use of a prospective protocol to retrospectively analyze the data. Your new analysis of that data should be submitted as an amendment to the NDA. [We thank you for your recent submission of this material].

REGARDING THE OBJECTIVES SECTION, Page 3

As we view this section, it is a statement of your goals for the meeting; hence, we do not have any direct comments on this section.

REGARDING THE DISCUSSION OF CONTROLLED CLINICAL STUDIES, Page 4

1. As previously indicated in our October 28, 1994 letter, E002 is supportive of efficacy. Also, noted in that letter and in the above 5th point, a second study is still needed.
2. The expertise of Drs. Parsons, Sant, and Hanno is not in question. The issue is that their participation in both E001 and E002 means that the studies are not independent. Also, the results of the trial are driven by Parsons' data. Therefore, the trials are not independently replicated. The summary slide presented by your staff at the meeting confirmed this finding and showed that the benefit was driven by the Parson's data. Thus, we did not agree to meet further on this issue. As always, if you have statistical methodology points, they can be submitted for consideration.

REGARDING THE COMPASSIONATE USE DATABASE, PAGE 4-5

1. In reference to potential conclusions from the compassionate use data, we do not share your opinion that the existing compassionate use database clearly demonstrates relief of the pain symptoms as a measure of success or that a percentage of patients who respond to Elmiron continue to respond for several years. This is an open question and the extent to which the data support the effectiveness must await the review of your new analysis.
2. Regarding analysis of the compassionate data we indicated that pre-submission discussions on format, protocol design and the type of analysis could be useful. Subsequent meetings may be considered after an appropriate analysis has been completed and reviewed.

ADDITIONAL CLINICAL STUDIES, Page 5

In addition to the above and the possibility of other studies, representatives from BNP stated that you did not plan to do any other pre-approval study, and that a placebo withdrawal study is not one of your choices for a future "post-approval" clinical study. We understand that responder predictors could be difficult to identify and that such a study might have to overcome several obstacles. However, we maintain that such a

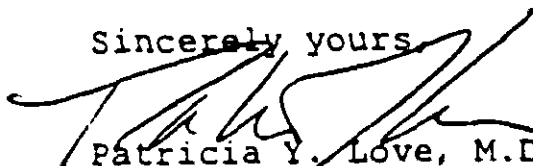
study would be very useful in defining the true pharmaceutical effect of Elmiron in IC patients. Until Elmiron is approved, we can not agree to the status of any future studies.

As requested, a copy of our minutes of that meeting is enclosed.

Should you have any questions, please contact:

Ms. Julie Rhee
Consumer Safety Officer
Telephone: (301) 443-7515

Sincerely yours,



Patricia Y. Love, M.D., M.B.A.
Director, Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: FDA Meeting Minutes of February 16, 1995.

cc:Original NDA 20-193
HFD-160/Div. Files
HFD-100/DepDir/Botstein
HFD-160/DivDir/Love
HFD-713/Smith
HFD-713/Davi
HFD-160/SCSO/Cheever
HFD-161/CSO/Rhee

drafted: Rhee/5-10-95 elmironm.ltr
revised: Cheever/5.30.95
Acknowledgements: Cheever, 5.30.95; Love, 6.7.95
F/T by: Wilson, 6.8.95
Acknowledgement: Cheever, 6.23.95
F/T by: Wilson, 6.23.95

General Correspondence

Division of Medical Imaging, Surgical and Dental Drug Products

Meeting Minutes

Drug: NDA 20-193 Elmiron

Date: February 16, 1995

Attendees:

FDA:

Paula Botstein, M.D., Deputy Director, ODE I
Patricia Love, M.D., Division Director, DMISDDP
Paul Waymack, M.D., Medical Officer, DMISDDP
Eric Sheinin, Ph.D., Supervisory Chemist, DMISDDP
Patricia Stewart, Chemist, DMISDDP
Nancy Smith, Ph.D., Group Leader, Div. of Biometrics
Ruthanna Davi, Statistician, Div. of Biometrics
John Hunt, Group Leader, Division of Biopharm.
Jack McCormick, M.D., Office of Orphan Products
Erica McNeilly, Office of Orphan Products
James Cheever, D.M.D., Supervisory CSO, DMISDDP
Julie Rhee, Consumer Safety Officer, DMISDDP

Baker Norton Pharmaceuticals, Inc.

Barry Strumwasser, President
Ed Mitchell, Ph.D., V.P., Regulatory Affairs
John Whisnant, M.D., Senior V.P., R & D
Fred Sherman, M.D., Medical Director
Marcia Samuels, Project Manager
Steve Carrier, Ph.D., Senior Director, Biometrics
Phillip Frost, M.D., IVAX
Jane Hsiao, Ph.D., IVAX

Consultants:

Granlum Sant, M.D., Chief of Urology, Tufts University
Stacy Childs, M.D., Prof. of Urology, Univ. of Alabama
Debra Slade, Exec. Director, Interstitial Cystitis Assoc.
Vicky Ratner, M.D., President, Interstitial Cystitis Assoc.

=====
This meeting was requested to discuss a not approvable (NA) letter, which was issued to the company on October 28, 1994.

Baker Norton Pharmaceuticals (BNP) stated that there is no known therapy for interstitial cystitis (IC) and, therefore, they are seeking a limited approval of Elmiron for relief of pain in IC patients who meet NIH diagnostic criteria and who have not responded to DMSO therapy.

Dr. Ratner and Ms. Slade expressed their frustration in developing or analyzing the data because there are not any identified disease or predictor markers. Also, noted was the historic difficulty in diagnosing IC.

BNP also noted their frustration because of the long review process and because they have a large number of patients on a compassionate program. Cost is also an issue.

We re-informed the company that we require two independent and well-controlled studies for an NDA approval. As already noted in the non-approvable letter, so far, we only have one adequate and well controlled trial (E002). This is because the two studies in this NDA are not independent. The majority of the data in both studies are primarily from the same investigators. Also, the statistical significance is driven by those investigators. In an attempt to reanalyze this, when these investigators are removed from either study, the statistical significance over placebo is lost. Thus, their two trials are really only one trial.

BNP responded that there are very few physicians who treat IC and that by throwing out the second trial we are ignoring the results of a qualified expert. We indicated that we need replication of an adequate study. This is in part needed in order to show that other physicians can safely use the product. So far their data shows that one physician can use Elmiron; the results from the other physicians do not show improvement. The sponsor showed a slide with pooled data from all investigators in order to support their position. This slide confirmed our point that the data is driven by one physician (Parsons).

BNP also noted that not all patients respond to the Elmiron; however, to date they do not have any predictive data. The patient advocate also noted that the most significant benefit was pain and the urination frequency. The patient advocate and the consulting physicians noted personal experience with Elmiron.

We suggested that BNP develop a design to address responders and non-responders. This is particularly of value in the evaluation of the drug product that is heavily affected by the patient's opinion.

BNP said an IC patient's quality of life is worse than the end stage of renal failure patients. We informed them that although we are sympathetic to the problem, we have to have a database before we can approve a drug product.

The discussion turned to how to obtain approval of the NDA. We repeated that the fact that we can accept trial E002 and we need a new second one. We were prepared to discuss the trial design options that the sponsor included in their pre-meeting package. BNP, however, stated that they were not going to do a new study. The trial designs in the package were for background and they did not wish to discuss them. BNP felt that the compassionate use

experience in close to 1000 patients was sufficient to show that the product worked. There were patients were on drug for a long period of time (about 5 years).

BNP indicated that if the product was approved on a limited basis, then they would do phase IV studies to explore the dose response and dosing regimen; e.g., what is the optimal dose, how often should it be given. They also feel that a randomized withdrawal design to identify responders will cause patient relapses. They also noted that they are willing to conduct a Phase 4 study on the mechanism of Elmiron on the bladder surface. BNP stated that they plan to conduct studies on urinary concentration, dose comparison between 300 and 600 mg/day, and urinary alkalization supplementation as Phase 4 studies.

During the discussion, BNP suggested that there may be additional data in the compassionate use database that could be re-analyzed. If so, perhaps it could form the basis of the second trial. We noted that this will be the third reassessment of old data that was twice deemed inadequate; that is a sponsor risk. We are willing to work with them to develop an appropriate prospective protocol to retrospectively look at the compassionate data. We recommended a follow-up meeting between BNP and FDA statisticians and clinical reviewers.

[NB: In discussing the compassionate use data, we indicated that it was reviewed during the first NDA and was insufficient. In the resubmission, because the data was open label, it again was reviewed for safety. The company noted the precision with which the case report forms were filled would support the data. The FDA noted that in order for the compassionate data to qualify as a trial, it will need a different type of statistical analysis. BNP noted that a reanalysis of the compassionate patients was submitted. Again, we stated that it was not analyzed in the manner of a trial; therefore, in its present condition it was reviewed for safety.]

If BNP has any other data that was not submitted it should also be submitted.

We reiterated that our best recommendation is that they conduct a new trial; also, we are not sure if the compassionate database reanalysis will be useful. We, however, agreed to work with them to analyze and review the data.

We offered to place this application on our project management plan for tracking and to give it a high priority.

We will call Dr. Mitchell concerning the next meeting time frame.

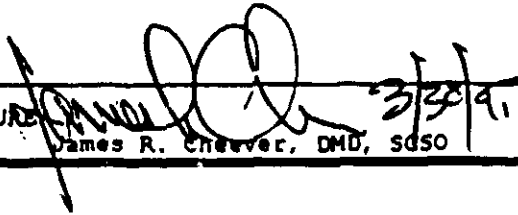
Conclusion:

1. The NDA remains not approved.
2. We reiterated that we already accept study E002 as one pivotal study. A second study is needed.
3. We will review their compassionate use database. Prior to that review, we suggest that the statisticians at the Agency and the company discuss the data and an appropriate analytical protocol.
4. If they have any other data they wish to submit, we agreed to review it.
5. We will put this application on a project management plan.


Julie Rhee

cc:Orig NDA
HFD-160/Div File
HFD-100/Botstein
HFD-160/Love
HFD-713/Smith
HFD-161/Rhee
R/D by: Rhee 3-20-95
Concurrence: Cheever 3-21-95/Waymack 3-21-95/Davi 3-23-95/
Smith 3-23-95/Love 4-6-95
F/T by: Rhee 4-14-95 win6.0c:20193met.min

Meeting minutes

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE March 30, 1995		
I returned Mr. Mitchell's call (x2) requesting information on the outcome of our internal meeting concerning the value of their open-label compassionate-use data base.	NDA NUMBER 20-193		
I stated that we had met and would be requesting some further information regarding the existing data base which would include further analyses and the raw data. I committed to forwarding a fax of our requests/comments in a matter of days. I asked him to call back by mid-week if he had not heard from us. Following the fax, we will contact him at a working level (ie stats to stats) regarding the specifics contained in our fax communication.	IND NUMBER		
I also discussed in non-specific terms our differing viewpoint of some events and conclusions emanating from our last meeting. I stated that we would formally reply with our understanding of the meeting's outcome in a letter at a later date in order to correct the official record of events. He appeared to accept the above plan with no objection and acknowledged the need to keep the record complete. The conversation ended cordially.	TELECON		
cc: NDA 20193 HFD-160/LOVE/WAYMACK/RHEE HFD-713/SMITH	<table border="1"> <tr> <td data-bbox="1206 947 1443 1063"> INITIATED BY ☒ APPLICANT/ SPONSOR ☐ FDA </td> <td data-bbox="1443 947 1687 1063"> MADE ☒ BY TELEPHONE ☐ IN PERSON </td> </tr> </table>	INITIATED BY ☒ APPLICANT/ SPONSOR ☐ FDA	MADE ☒ BY TELEPHONE ☐ IN PERSON
INITIATED BY ☒ APPLICANT/ SPONSOR ☐ FDA	MADE ☒ BY TELEPHONE ☐ IN PERSON		
	PRODUCT NAME ELMIRON		
	FIRM NAME BAKER NORTON		
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Ed Mitchell Reg Affairs		
	TELEPHONE 305/770-5250		
SIGNATURE  James R. Cheever, DMD, SDO	DIVISION HFD-160		

NDA 20-193

OCT 28 1994

Baker Norton Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404

Attention: Jane H. Hsaio, Ph.D.
Chief Regulatory Officer

Dear Dr. Hsaio:

Please refer to your June 11, 1991, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elmiron (pentosan polysulfate sodium).

We acknowledge receipt of your amendments and correspondence dated August 28 and 30, September 9, 10, and 11, and October 3 and 28, 1991; January 22 and 27, June 2 and 22, November 9, and December 10, 1992; February 4, March 2, April 6 and 20, May 26, June 2, and July 7 and 20, 1993; and February 11, 1994. We also acknowledge receipt of a correspondence (undated) on February 17, 1994. Additionally, we refer to our not approvable letter dated January 27, 1993.

We have completed our review and find that the information presented is inadequate and that the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b) of the implementing regulations.

PART I: Summary of Not-Approvable Issues

Clinical:

1. Your amendment dated July 7, 1993, consisted of a reanalysis of clinical studies E001 and E002 in patients with interstitial cystitis. We have reviewed this amendment to determine whether the reanalysis can provide sufficient clinical evidence of effectiveness and safety.

Three investigators participated in studies E001 and E002 and contributed the majority of the patients in each study; i.e., they contributed 75% of the patients in study E001 and 57% of the patients in study E002. Because these three investigators played such a major role in the results of both studies, these studies cannot be considered as two independent studies.

Furthermore, after removing the patients contributed by the largest of these three investigator sites, neither study has sufficient statistical power to demonstrate effectiveness for any of the six primary outcome measures. Also, it is not clear from the information submitted if patients may have participated in both studies.

2. We evaluated each study to determine if it demonstrated safety and effectiveness of Elmiron in patients with interstitial cystitis. After statistical accounting for the multiple comparisons made of the data, study E001 achieved statistical significance for one of your six primary outcome measures of effectiveness. This outcome measure was "decrease in bladder pain based on the change in rating scale from baseline to endpoint". Statistical evidence of effectiveness was not achieved for the other five outcome measures of effectiveness. These measures were "overall improvement based on patient evaluation (global)", "overall improvement based on investigator evaluation (global)", "decrease in urgency based on the change in rating scale from baseline to endpoint", "improvement in bladder pain based on patient overall assessment (global)", and "improvement in urgency based on patient overall assessment (global)". Therefore, study E001 does not provide adequate evidence of effectiveness of Elmiron in patients with interstitial cystitis.

After statistical accounting for the multiple comparisons made of the data, study E002 achieved statistical significance for two of your six primary outcome measures of effectiveness. These outcome measures were the "overall improvement based on investigator evaluation (global)" and "improvement in bladder pain based on patient overall assessment (global)". Statistical evidence of effectiveness was not achieved for the other four primary outcome measures of effectiveness. These measures were "overall improvement based on patient evaluation (global)", "decrease in urgency based on the change in rating scale from baseline to endpoint", "decrease in bladder pain based on the change in rating scale from baseline to endpoint", and "improvement in urgency based on patient overall assessment (global)". Therefore, study E002 provides some evidence of effectiveness of Elmiron in patients with interstitial cystitis.

Thus, your database has only one adequate and well-controlled clinical study showing effectiveness and safety. We, therefore, recommend that you conduct an additional adequate and well-controlled clinical study designed to show effectiveness and safety. This study, if clearly positive and otherwise acceptable, plus study E002, would provide sufficient evidence for approval. We have the following recommendations for the new study:

1. Include a sample size large enough to assure adequate power to detect a clinically significant difference in effectiveness between the groups compared. Strategies should be included to encourage patients to remain in the study until the end of the treatment period and to return for a final evaluation at the scheduled time even if they have dropped out of the study before 3 months.
2. Use an improved scale for the measures of effectiveness. In studies E001 and E002, the measures of effectiveness were reported on a six point scale [from -1 (worse) to 4 (100% improvement)]. The case report form asked only four questions about effectiveness. It is not clear how this four point scale was translated into a six point scale. Although certain answers to these four questions could be interpreted as fitting additional categories of no change or worsening; it is preferable to clarify the questions.
3. Conduct the study in a homogeneous population or in one that is adequately randomized upon variables that could affect outcome; e.g., residual void volume, frequency and severity of urinary urgency. The outcome variables should not be redundant. We recommend that you pre-select one or two primary outcome variables. The statistical plan should include a method for adjustment for multiple comparisons if it is decided to utilize multiple outcome measures.
4. Exclude any investigators who participated in study E002.

Chemistry, Manufacturing, and Controls:

1. Please submit drug substance stability data collected to date. Also, explain why testing was not performed at 18 months.
2. The drug substance control specification for Loss on Drying should be stated as % rather than "report value (%)". Also, please comment on the results obtained during the stability studies; results as high as 8.6% were reported for the 25°C - 30°C samples. Future stability studies should be run at the target temperature $\pm 2^\circ\text{C}$, e.g., $30^\circ\text{C} \pm 2^\circ\text{C}$.
3. The specification for Transparency of the drug substance is %. The actual results should be reported, not "meets test".
4. Please provide additional stability data on the drug product manufactured by Baker Norton at Miami, Florida facility. Data on at least three lots will be required to establish an expiration dating period.
5. Letters of Authorization for DMF's should be provided which state specifically that they can be referenced on behalf of Baker Norton Pharmaceuticals, Inc.

Environmental Assessment (EA):

1. The EA is a public document that will be available for review. Information required under 21 CFR 25.31a should be contained in the EA. This information includes material safety data sheets for the drug substances and/or drug product and data summary charts for the tests performed in support of the EA. Confidential or proprietary information should be placed in appendices clearly marked confidential. However, confidential information should be summarized to the extent possible and included as part of the EA in accordance with 21 CFR 25.30(b).

In support of this EA, you reference a Drug Master File (DMF). Since a DMF is a confidential document, please submit a Letter of Authorization from its holder permitting us to reference it on your behalf. In order to support this EA or any confidential portion of the EA, you must extract applicable data from the DMF, with the holder's authorization.

2. Section titled: Description of the proposed action.
 - a. The medical purpose of this drug product and the reason for its review status as an orphan product should be submitted.
 - b. Discussion of sites for the manufacturing, packaging, labeling, etc., does not state whether any additional processing or reprocessing of starting materials, intermediates, or final drug product takes place. Please provide information.
 - c. The EA fails to disclose any outside facilities (both company controlled and outside contractors), if any, which may be used for packaging, or repackaging, processing or reprocessing, labeling warehousing, disposal of any starting or intermediate materials, active drug substance or final drug product. Please submit descriptions which should include the types of environments present at and adjacent to these locations.
 - d. You have not submitted any relevant information on site descriptions/capabilities, environmental permitting, etc., as appropriate for facilities operated by or contracted by you. Site descriptions including the types of environments present at and adjacent to these locations should be submitted.
3. Section titled: Identification of chemical substances that are the subject of the proposed action.
 - a. Adequate physical and chemical data to characterize the drug substance were not submitted. Please refer to 21 CFR 25.31a(a)15(a) and (b) for minimal information required.
 - b. Material Safety Data Sheets (MSDS's) for all starting materials, as well as for the active drug substance and final drug product should be submitted. MSDS's should include all available ecotoxicological information.
 - c. A description of the manufacturing process and a process flow diagram for the final drug product should be submitted.

- 3) Statements and certifications regarding compliance with applicable emission requirements (including occupation) at the local, state, and federal level. ..
 - c. The methods of disposal and outside contractors which may be used for mitigation of waste and disposal of out-of-specification and/or recalled drug product should be designated.
 - d. Please develop a 5-year marketing plan and identify which year has the largest projection for production of the drug product.
5. Additional information should be provided in the following sections:
- a. Fate of emitted substances in the environment;
 - b. Environmental effects of released substances;
 - c. Use of resources and energy;
 - d. Mitigation measures; and
 - e. Alternatives to the proposed action.
6. The references submitted are incomplete. Appended references should also include the following information:
- a. MSDS's for the active drug substance and final drug product; and
 - b. Any available references to toxicological and ecotoxicological properties of the active drug substance and final drug product.

PART II: Other

Chemistry, Manufacturing, and Controls:

We have the following comments about methods validation. At the present time, it is the policy of the Center not to withhold approval because of the deficiencies in the methods validation. We expect your cooperation to resolve the following deficiencies:

- a. Please provide evidence that the infrared identification test is specific for the active ingredient in the drug product which contains approximately 1% microcrystalline cellulose. Is a preliminary separation step needed?

- b. Dissolution time should be written into the procedure for operating the dissolution apparatus. The time is listed under the specifications on page 199.
- c. Apparatus #4 (pages 212 and 213) is listed as mL pipettor". This should be rather than
- d. The option of using glass pipets in place of the pipettor is given in the dissolution test. The procedure as written uses "pipettors". Adequate directions should be provided in the written procedure for making dilutions using a glass pipet.

Biopharmaceutical:

- a. The to-be-marketed formulation should, if possible, be used in the new clinical study in order to avoid a bioequivalence issue.
- b. Your July 7, 1993, amendment included a new protocol (IX 106-063A) synopsis to address the bioavailability and pharmacokinetic data which were mentioned in our January 27, 1993, not approvable letter. This protocol and related issues will be addressed in a separate IND letter.

We recommend that you submit proposed protocols (with case-report forms and statistical plan) for our review and comment prior to initiation of a study. We encourage you to meet with us when you have developed a draft protocol. Our meeting about the design of clinical studies of interstitial cystitis on March 19, 1993, was useful and we urge you to proceed with the ideas developed during that meeting when you draft new protocols. We stand ready to work with you on this orphan drug for a serious medical disease. Also, we urge you to consult the Agency regarding any questions on Environmental Assessments and any proposed testing requirements.

We also wish to remind you that a full safety update must accompany your NDA resubmission.

We reserve comment on the labeling for the drug product until the application is otherwise approvable.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the Food and Drug Administration may take action to withdraw the

Page 9
NDA 20-193

application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

Should there be any questions, please contact Ms. Julie Rhee, Consumer Safety Officer, at (301) 443-5818.

Sincerely yours,

Paula Botstein MD 10/28/94

Paula Botstein, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 28-193

7 OF 7

cc:OrigNDA 20-193
HFD-160/DivFile
HFD-160/DivDir/Love
HFD-130/District Office
HF-1/Merkatz
HF-35
HFD-82
HFD-100
HFD-340
HFD-638
HFD-735
HFD-160/MO/Waymack
HFD-160/SChem/Sheinin
HFD-160/Chem/Stewart
HFD-160/Pharm/See
HFD-713/Smith
HFD-713/Turney
HFD-713/Sobhan
HFD-100/Mueller
HFD-426/Hunt
HFD-161/CSO/Rhee

R/D by: Rhee 5-6-94

Acknowledgements: Cheever/Waymack/Stewart/Sheinin/See/
DeWitt- 5.10.94; Rhee/Hunt- 5.11.94; Mueller- 5.12.94;
Vincent-5.13.94

F/T by: CWilson- 5.18.94

Rev by: Botstein 8-16-94

Rev by: Botstein/Love/Waymack/NSmith 10-25-94

Re R/D by: Rhee 10-25-94 a:revelm2.na

Acknowledgements: Cheever/Waymack 10-26-94

F/T by: Rhee 10-26-94

Edited by: Botstein 10-26-94

Edited by: Botstein 10-28-94

m 10-28-94

a:revelm5.na

F/T by: T.Russell 10-28-94

*Michael
JG 10/28/94*

Not Approvable

NDA 20-193

21.
FEB 28 1994

Baker Norton Pharmaceuticals, Inc.
8800 Northwest 36th street
Miami, Florida 33178-2404

Attention: Jane Hsiao, Ph.D.
Vice President

Dear Dr. Hsiao:

Reference is made to your new drug application for Elmiron Capsules, 100mg. We acknowledge receipt on February 14, 1994, of your amendment dated February 11, 1994.

We consider this a major amendment under 21 CFR 314.60 of the regulations, and we have determined that 60 additional days will be required for its review. The new due date is April 15, 1994.

If you have any questions, please contact:

Ms. Julie Rhee
Consumer Safety Officer
(301) 443-5818

Sincerely yours,

 2/25/94
Patricia Y. Love, M.D., M.B.A.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Orig. NDA 20-193

HFD-160/Division File

HFD-161/CSO/Rhee in 2-24-94

R/D by: Yazdani-02-18-94

F/T by: AChapman-02-24-94 NDA\N20-193.3EX

EXTENSION OF REVIEW PERIOD

JUL 21 1993

NDA 20-193

Baker Norton Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404

Attention: Edward R. Gubish, Ph.D.
Regulatory Affairs

Dear Dr. Gubish:

Reference is made to your new drug application for Elmiron (Pentosan polysulfate sodium). We acknowledge receipt on July 9, 1993, of your amendment dated July 7, 1993.

We consider this a major amendment under 21 CFR 314.60 of the regulations, and we have determined that 120 additional days will be required for its review. The new due date is November 6, 1993.

If you have any questions, please contact:

Ms. Julie Rhee
Consumer Safety Officer
(301) 443-5818

Sincerely yours,



Patricia Y. Love, M.D., M.B.A.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA 20-193
HFD-160/Division File
HFD-161/CSO/Rhee on 7-19-93
F/T by: AChapman-07-19-93
Acknowledgements: Cheever-07-15-93
C:\WP51\FILES\NDA\N20-193.2EX
EXTENSION OF REVIEW PERIOD

JAN 27 1993

Baker Norton Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404

Attention: Edward R. Gubish, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Gubish:

Reference is made to your new drug application dated June 11, 1991 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elmiron (pentosan polysulfate sodium).

We also acknowledge receipt of your amendments and correspondence dated August 28 and 30, September 9, 10 and 11, October 3 and 28, 1991; and January 22 and 27, June 2 and 22, November 9, and December 10, 1992. The December 10, 1992, amendment provides for the information on the manufacturer change from

and is currently under review.

We have reviewed your application and find that the information presented is inadequate and that the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b) of the implementing regulations. The deficiencies are as follows:

Clinical

The application as submitted lacks substantial evidence consisting of adequate and well-controlled investigations as defined in 21 CFR 314.126 that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically, the analysis of the results of the submitted studies are not adequate to assess the effects of the drug.

1. The analysis does not assess the comparability of the test and control groups with respect to pertinent variables and the effects of any interim data analysis performed.
 - a. We recommend that you provide a "per protocol" analysis for all variables. This analysis should exclude patients without pain on entry and exclude

patients at time points when no evaluation was performed.

- b. We also recommend that you provide an "intent to treat" analysis for all variables. This analysis should include all patients enrolled into the study and followed for all time points possible.

If the results of the "per protocol" and the "intent to treat" analysis are different, an explanation should be provided.

If the drug product is not considered to be equally effective in all patients with interstitial cystitis, then appropriate subgroup analyses should be performed which identify subpopulations in which the drug product is effective.

2. Additional support is needed to justify the statement that the relief of symptoms may not be experienced until after 6 to 8 weeks of therapy. In studies the time course of relief of symptoms in the active treatment group observed appears equivalent to the time course of relief of symptoms observed with the placebo therapy. This rate of relief of symptoms would, therefore, seem to represent the natural history of the disease and not to reflect therapy.
3. One purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences. Based on the analyses submitted for studies E-001 and E-002, there appears to be significant investigator interaction. The results obtained by the first investigator listed in each study are significantly different than the results obtained by each of the other investigators in the studies. In the absence of an adequate explanation for these differences, studies E-001 and E-002 cannot be considered to be adequate and well-controlled. We recommend that an additional clinical investigation utilizing investigators not included in previous studies be conducted and submitted as part of any amending of this application.
4. We recommend that you consider carrying out an additional study to demonstrate effectiveness of the drug. A powerful type of study which has been used to demonstrate effectiveness for other orphan drugs is a blinded, randomized withdrawal study of patients

believed to have received benefit from the drug. One group would continue Elmiron and the other would get placebo. Rescue procedures could be built into the study.

If the application is amended, we request that you submit complete case report forms and tabulations for all patients in studies E-001 and E-002.

Biopharmaceutical

The bio-data submitted has not adequately described the bioavailability/pharmacokinetics of Pentosan Polysulfate (PPS) in order to comply with 21 CFR 312.21 and is not adequate to support its approval as well as support its labeling. Please contact Dr. Daniel Gordin of the Division of Biopharmaceuticals at (301) 443-3520 to discuss further requirements and study protocol designs.

We reserve comments on the labeling for the drug product until the application is approvable and all deficiencies have been satisfied.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, should you so desire, you may request an informal conference with members of the Division of Medical Imaging, Surgical and Dental Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting is to be requested at least 15 days in advance. If you wish this conference or a telephone report, please call Ms. Julie Rhee, Consumer Safety Officer, at (301) 443-5818.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the Food and Drug Administration may take action to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

Page 4
NDA 20-193

Should there be any questions, please contact Ms. Julie Rhee,
Consumer Safety Officer at (301) 443-5818.

Sincerely yours,

Paula Botstein MD 1/27/93

Paula Botstein, M.D.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
and
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:OrigNDA 20-193

HFD-160/DivFile

HFD-130/JAllen

HF-35

HFD-82

HFD-100

HFD-340

HFD-638

HFD-735

HFD-SChem/Sheinin

HFD-160/Chem/Stewart

HFD-160/Pharm/Wilson

HFD-161/CSO/Rhee

R/D by: Rhee 1-14-93

F/T by: AChapman 01-21-93

Not Approvable

a:20193elm.na

M 1/27/93

NDA 20-193

Baker Norton Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404

Attention: Edward R. Gubish, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Gubish:

Reference is made to your new drug application for Elmiron Capsules, 100mg. We acknowledge receipt on December 11, 1992, of your amendment dated December 10, 1992.

We consider this a major amendment under 21 CFR 314.60 of the regulations, and we have determined that 120 additional days will be required for its review. The new due date is April 11, 1993.

If you have any questions, please contact:

Ms. Julie Rhee
Consumer Safety Officer
(301) 443-5818

Sincerely yours,

Paula Botstein MD 12/14/92

Paula Botstein, M.D.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
and
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA 20-193
HFD-160/Division File
HFD-161/CSO/Rhee *12-17-92*
HFD-161/Applications Examiner/Jenkins
R/D by: CYazdani 12-14-92
F/T by: AChapman 12-17-92
C:\WP51\FILES\NDA\N20-193.EXT
EXTENSION OF REVIEW PERIOD

12/14/92

~~J. Rhee~~
J Rhee

JUN 25 1991

NDA 20-193

Baker Cummins Pharmaceuticals, Inc.
8800 Northwest 36th Street
Miami, Florida 33178-2404 .

Attention: Jane H. Hsiao, Ph.D.
Vice President, Quality Assurance
and Regulatory Affairs

Dear Dr. Hsiao:

We have received your new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: ELMIRON (pentosan polysulfate sodium)
Capsules 100mg

Date of Application: June 11, 1991

Date of Receipt: June 19, 1991

Our Reference Number: NDA 20-193

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)(1) of the Act on August 18, 1991 in accordance with 21 CFR 314.101(a).

If the application is filed, the due date is December 16, 1991. Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact:

Ms. Julie Rhee
Consumer Safety Officer
(301) 443-3500

Sincerely yours,

Warren Rumble 6/25/91

Warren Rumble
Chief, Project Management Staff
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA 20-193
HFD-160
HFD-161/JRhee
HFD-161/DJenkins
R/D by: COeur 6/21/91
R/D Init. by:WRumble 6/ /91
F/T by: LParcover 6/ /91
Wang #4379N

ACKNOWLEDGEMENT OF ORIG. NDA

Meeting Minutes

**Division of Medical Imaging,
Surgical and Dental Drug Products (HFD-160)**

NDA 20-193 Elmiron (pentosan polysulfate sodium)

Date: March 19, 1993

Sponsor: Baker Norton Pharmaceuticals

Indication: For Interstitial Cystitis

Attendees:

FDA:

Paula Botstein, M.D., Acting Director, DMISDDP &
Deputy Director, ODE I
Wiley Chambers, M.D., Division of Anti-Infective
Tony Carreras, M.D., Division of Anti-infective
Ralph Harkins, Ph.D., Division of Biometrics
James Gebert, Ph.D., Division of Biometrics
Peter Vaccari, Orphan Drugs
Dan Gordin, Ph.D., Division of Biopharm
Julie Rhee, Consumer Safety Officer, DMISDDP

Baker Norton Pharmaceuticals:

Ken Duchin, Ph.D., Senior Director, Clinical Pharmacology
Ed Gubish, Ph.D., Vice President, Regulatory Affairs
Fred Sherman, M.D., Medical Director
John Whisnant, M.D., Vice President, R & D

Consultant:

Lowell Parsons, M.D., Urologist
Kay Hart, Statistician

Purpose:

To discuss January 27, 1993, Not Approvable letter.

Meeting Minutes:

1. Pentosan polysulfate sodium is excreted in urine according to the firm.
2. We asked the company to conduct studies for hemorrhagic cystitis and proctitis--currently, the NDA does not include these indications. The company agreed. We indicated that they could do a tight trial for efficacy on these indications.

Biopharm:

1. We expressed our concern that 2 different formulations were used in the clinical studies, and therefore, did not demonstrate bioequivalence. The company informed us that the active portion of the formulation did not change--only excipients were changed. They will submit full information on the formulations and dissolution data to the file.

Clinical:

1. Even though animal studies demonstrated that the drug product is safe at higher doses, the company wants to wait until dose escalating study is completed before they study with higher doses.
2. The company listed the following reasons as the difficulties associated with the studies:
 - a. Orphan disease,
 - b. Hard to evaluate emotional aspects associated with this disease, and
 - c. NIDDK defines the disease by symptoms only. But the company stated that 70% of the disorder associated with this disease can not be defined by symptoms only.
3. We inquired about the discrepancies in study results even though the studies were conducted by the same investigator. The firm replied that the discrepancies were dependent on whether or not the patient had cystoscopy done.
4. A randomized placebo withdrawal will work if patients are kept blinded. We recommended that they randomize responder patients to the current dose vs 1/4 of the current dose and conduct urine concentration study.
5. Is there a center effect in the study since the Protocol E-002 has a better response rate? We, also, indicated that E-002 had a different formulation.
6. In order to sort out variables, the company was told they need a larger sample size. However, the company said it is difficult to have a larger sample size because interstitial cystitis (IC) is an orphan disease. They, also, mentioned the disease varies patient to patient.
7. We informed the company that the database generated from the emergency IND's do not provide information to be used for efficacy evaluation.

8. The firm described IC as a progressive disease. For an example, there is a significant difference in bladder capacity depending on how long the patient had the disease.
9. The company estimates the IC patient population in U.S. to be between 20,000 to 90,000 and the efficacy rate to be about 30%.
10. With non-responder patients, we recommended that they study the current dose as well as higher doses. However, the firm will have to be ascertain that the patients in this study are non-responder.
11. The company indicated that they might consider concentrating on urinary concentration rate study.
12. The firm stated that getting right patient is heavily biased by investigators.
13. We informed the company that Elmiron does not meet treatment IND criteria for treating radiation cystitis and proctitis. Also, we informed them that we will no longer grant emergency IND's for these 2 indications. The firm agreed to study these indications.

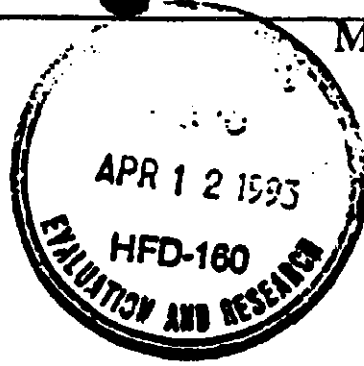
Statistical:

1. The firm will have to pay penalty for performing unplanned interim analysis.
2. The firm needs to specify the primary endpoint and/or have to adjust multiple endpoints.
3. Survival analysis should be done if they want to claim the ratio of improvement over time as an efficacy.
4. The company's statistician will contact Dr. Harkins to discuss issues regarding the global score, survival analysis, and interactions between centers and investigators.

Conclusion:

1. Study higher doses.
2. Specify the primary endpoints.
3. Reanalyze clinical trial data.

4. Submit information on the 2 different formulations and their dissolution data.
5. We will no longer grant emergency IND's for radiation cystitis and proctitis. The company agreed to submit protocols on these 2 indications.
6. They will call Dr. Harkins to discuss global score, survival analysis, and interactions between centers and investigators.



Date April 9, 1993

From Chemist, Chemistry Branch
Southeast Regional Laboratory (HFR-SE660)

Subject NDA 20-193, Elmiron Capsules

Firm: Baker Norton (Cummin) Pharmaceuticals
Miami, Florida 33178

To Patricia Stewart, Reviewing Chemist, Office of Drug Evaluation, CDER (HFD-160)

Thru Sander W. Bellman, Director, Chemistry Branch
Southeast Regional Laboratory (HFR-SE660) SB 4/9/93

The Southeast Regional Laboratory recently received a request from our Orlando District office regarding sample sizes to be collected for the subject NDA methods validation. Our review of the application and analytical methodology for both the finished product and drug substance resulted in several questions that we believe need to be addressed.

1. We do not find any reference in the application to lot "D-4" for the drug substance you specify to collect on form 2871a. We find references to lots B-10 (page 8), B-8 (page 11), and D-3 (pages 13 & 14), but no reference to lot D-4. Please specify if this is accurate or which lot should be collected.
2. We consider the firm's identification test for the active ingredient in the finished dosage form to be scientifically unsound. The firm's procedure calls for an IR curve on a blended portion of the capsule composite without any preliminary separation or isolation of the active drug substance. According to their formulation, about 10% of this capsule composite is microcrystalline cellulose which would contribute to the IR spectrum. It would be interesting to know what type of IR spectrum would be obtained with the microcrystalline cellulose alone.

We would recommend non-approvability of the application based only on our review of this identification test.

3. We also noticed in the Merck Index that the drug substance is optically active. This fact is also included in the manufacturer's certificate of analysis for the drug substance. Shouldn't the firm include a test for specific rotation for the drug substance?
4. It's our understanding that NDA's require two laboratories for method validation. The home district's (ORL-DO) servicing laboratory, in this case the Southeast Regional Laboratory, is generally one validating lab and DDA (HFH-300) CDER, St. Louis, usually is the second lab. You make no mention of a second validation lab on

Patricia Stewart
April 9, 1993
Page 2

Form 2871. May we assume that a second portion along with a portion for forensics should be forwarded to DDA as the second lab and also to perform the forensics testing? This appears to be the proper procedure and portions to be collected according to Compliance Program 7346.832 of 6/1/92.

5. We feel very strongly that a joint investigator/analyst team should conduct a pre-approval inspection and any necessary corrections to the methodology should be made prior to any methods validation work.

Please advise Orlando District, HFR-SE250, and Miami Resident Post, HFR-SE2575 of your decisions and answers to the above questions at your earliest convenience. Please copy the Southeast Regional Laboratory, HFR-SE660, with your response.


Kermit M. Floyd

KMF:mjw

REVIEWS COMPLETED

CSO ACTION:

LETTER

N.A.I.

CSO INITIALS

DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Office of Orphan Products
Development

Memorandum

DATE: October 22, 1992
FROM: Peter Vaccari, SCSO 
SUBJECT: Orphan Drug Status in COMIS of Pending NDAs
TO: Jim Cheever, Acting SCSO
HFD-160

NDA 20-193, Elmiron (pentosan polysulfate), filed with your division, is a designated orphan product. Please update the COMIS system with the character "V" in the chemical information field to reflect that this drug is an orphan product.

Thanks.



Record of Telephone Conversation



Date: 5/24/94

NDA/IND Number: 20-193

Telecon initiated by: N. See

Product name: Elmiron

Person contacted: Dr. Kamul Abdul at NTP

Telephone Number: (919) 541-7819

I contacted Dr. Abdul at NTP and informed him that I would be the division contact person in regard to NTP's toxicologic characterization of Elmiron. We briefly discussed the existing data and the types of additional studies that should be performed. Due to the antiquity and non-GLP status of much of the existing data, it was agreed that NTP should repeat any studies that are deemed critical to the success of the NTP effort. Such studies would include appropriate pharmacokinetic, genetic toxicology, and dose-ranging studies. It was also agreed that the proposed 2 generation reprotox. study would be useful, since much of the existing reprotox. data was derived from studies performed in the early 1960's and involved exposure by a route different from the route of administration proposed for clinical use (subcutaneous vs. oral). We next discussed the need to adequately characterize the test substance to ensure that it would be representative of the drug substance. I suggested that Dr. Abdul forward to me the information that he had concerning the test substance and stated that I would discuss it with the reviewing chemist of the Elmiron NDA. He agreed to this. We agreed that Dr. Abdul would send me protocols of the studies to be conducted with Elmiron (when available), and that I would communicate my thoughts concerning the protocols. I asked him to contact me if I could be of service, and to keep me informed. Dr. Abdul suggested that I travel to NTP to attend a meeting concerning the Elmiron project. The meeting would probably be held during the week of June 13, 1994. I stated that I would look into the matter, but that I doubted that division funds would be available. The conversation was quite cordial.

Norman A. See 5/24/94-

Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc: Orig. NDA 20-193
HFD-160 Div. File
HFD-160/Rhee
HFD-160/DeWitt
HFD-160/Bailey
HFD-160/See
HFD-160/Love
HFD-400/JFContrera

Co. Corres.

**BAKER NORTON
PHARMACEUTICALS, INC.**

8800 Northwest 36th Street
Miami, Florida 33178-2404
Telephone 305/590-2200
Facsimile 305/590-2252

NDA #20,193

November 9, 1992

Dr. Wiley Chambers, Director
Div. of Medical Imaging, Surgical and
Dental Drug Products (HFD-160)
Attn. Document Control Room #18B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

ORIGINAL

NEW CORRESP

NC

Re: NDA #20,193 for Elmiron

Dear Dr. Chambers,

The sponsor of the above-mentioned NDA, Baker Cummins Pharmaceuticals, Inc., has recently undergone an administrative name change. As of August 1, 1992 the corporate name now reads "Baker Norton Pharmaceuticals, Inc." This will not affect any of our responsibilities for this NDA.

Sincerely,



Edward R. Gubish, Ph.D.
Vice President, Regulatory Affairs

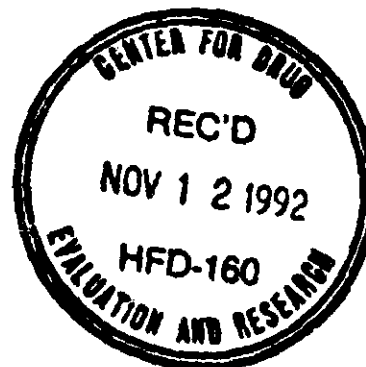
REVIEWS COMPLETED

SO ACTION:

LETTER N.A.I.

COMMENTS

DATE



August 31, 1994

Marlene Haifner, M.D.
Orphan Drug Products
FOOD AND DRUG ADMINISTRATION
5600 Fisher Lane
Rockville, Maryland 20857

RECEIVED

8500 Northwest 56th Street
Miami, Florida 33178-2404
Telephone 305/590-2200
Facsimile 305/590-2265

1994

Office of Orphan Products Development

Subject: *Elmiron[®] for Interstitial Cystitis*

Dear Dr. Haifner:

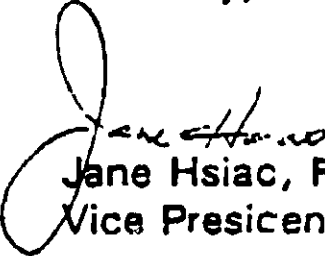
Thank you, Dr. McCormick and Mr. Vicarri for your interest and advice during the meeting with BAKER NORTON on August 26, 1994. We all recognize that interstitial cystitis is a devastating orphan disease and currently lacks adequate treatment. As Sponsor for a potential therapy for IC, BAKER NORTON has pursued an NDA approval including a major amendment which responded to the Agency's questions of early 1993. Your feedback that there are still outstanding issues on efficacy is very helpful. We appreciate your offer to facilitate a working meeting on clinical designs with Dr. Love and the reviewing division. The attached participant list and agenda is proposed for your discussion; we await confirmation of this important meeting. Proposed dates are September 19 or 20, September 8 or 9, or September 22-23, in order of preference.

We appreciate your advice regarding the focus and objectives for our meeting with the reviewing division. Our list of participants includes people with insight and expertise into the difficult problem of studying interstitial cystitis. We would bring urologic experts in interstitial cystitis not in order to discuss results of published trials, but to understand the complexity of this disease and confounding variables. We would invite patient advocate representatives not in order to plead for immediate drug approval, but to understand the disease and the implications and scheduling for the next steps in this process. We would bring statistical experts not in order to argue previous data but in order to understand the power, number requirements, and analyses required for any new trials. (We previously reviewed trial analyses in our March 1993, meeting with the division and we submitted the requested reanalysis of those trials in July 1993.)

August 31, 1994
Marlene Haffner, M.D.
Page 2

The present compassionate use program for Elmiron® availability continues to be a burden to this Sponsor and has been, in many cases, unacceptable to patients. We do have ideas regarding limited access, restrictive labeling, and post approval conditions if our discussions with the division reach that stage.

Sincerely,


Jane Hsiac, Ph.D.
Vice President

cc: Peter Vaccari, R.Ph., Office of Orphan Drugs, FDA, 5600 Fisher Lane, Rockville, Maryland 20857

WHD:ANTH ETTERS/MAF:INCLM

