Number of Pages Redacted 9

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

91 pages

draft document

(E)

IMMUNEX

Immunex Corporation
Regulatory Affairs
51 University Street
Seattle, WA 98101

Phone: 206 381-6266
Fax: 206 223-0468

FAX MESSAGE - PLEASE DELIVER IMMEDIATELY

Send to: Mr. Alvis Dunson, Project Manager Fax: (301) 594-0498

From: Mark W. Gauthier Date: March 30,2000

Total Number of Pages: 4 INCLUDING THIS PAGE

Re: NDA 19-297/S-022 NOVANTRONE (mitoxantrone HCl)
Revised Labeling

Dear Mr. Dunson:

Attached please find revised text for the package insert black box warning originally submitted in S-022 dated June 3, 1999. We received your comments on the package insert jointly reviewed by the Divisions of Oncology Drug Products and Neuropharmacological Drug Products and have incorporated your suggested changes and additions. During the teleconference that took place on March 28, the Medical Reviewer recommended we refine our draft language and submit it as an amendment to S-022. However, we are currently finalizing our responses to the approvable letter dated March 1, 2000, and plan to submit them to DNDP at the end of next week. We would like to confirm that we have adequately addressed your comments prior to submitting our response. Therefore, prior to formally amending S-022, we would appreciate receiving the Medical Reviewer's comments by Wednesday April 5, 2000. It is our understanding from Dr. Katz that the revised package insert included in our response to the approvable letter will be subject to re-review by the Oncology Division.

Revisions to the black box since the initial submission of S-022 are (refer also to your comments dated March 23, 2000):

1. The suggested language prohibiting intrathecal use has been strengthened beyond your recommendations.
2. An abbreviated statement regarding extravasation has been incorporated with a reference to WARNINGS.
3. The statement regarding cardiotoxicity has been expanded and now includes the specific nature of cardiotoxicity, probability of CHF, and risk factors that increase the likelihood of CHF.
4. A statement has been added regarding the risk of secondary leukemia. We do not feel that we can provide a quantitative estimate of the risk of AML based on current information available in the Immunex database (spontaneous event reports and clinical studies).

The attached document is still in draft form and subject to further revision prior to approval.

If you have any questions regarding the above, please contact me at your convenience at (206) 381-6266.

ncerely,

Mark W. Gauthier

Mark W. Gauthier

cc: Nancy Kercher
Teresa Wheelous, DNDP, fax (301) 594-2858

APPEARS THIS WAY
ON ORIGINAL

IMMUNEX

Immunex Corporation
Regulatory Affairs
51 University Street
Seattle, WA 98101

Phone: 206 381-6266
Fax: 206 223-0468

FAX MESSAGE - PLEASE DELIVER IMMEDIATELY

Send to: Ms. Teresa Wheelous Fax: (301) 594-2858

From: Mark W. Gauthier Date: March 30, 2000

Total Number of Pages: 5 INCLUDING THIS PAGE

Re: **NDA 21-120, Novantrone for Multiple Sclerosis**

COMMENTS:

Teresa,

Attached please find a copy of a facsimile that was sent to the Division of Oncology Drug Products today to address their comments on the NDA 21-120 draft package insert. I am providing a copy to you for information only.

If you require additional information, please contact me directly at (206) 381-6266.

Sincerely,

Mark W. Gauthier
Sr. Manager, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

immunex

March 24, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 21-120, Amendment No. 008
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
General Correspondence

Dear Madam or Sir:

Enclosed please find three copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. At the request of Ms. Teresa Wheelous, Project Manager, copies of four facsimile transmissions sent to various individuals are provided to assure that the file is up to date with all communications.

1. February 8, 2000: Request for teleconference with Biopharm reviewers sent to Ms. Teresa Wheelous. Teleconference scheduled for March 23, 2000, completed.
2. March 7, 2000: Protocols for in vitro metabolism studies sent to Dr. Raman Baweja for review and comment. Same information also faxed to Ms. Teresa Wheelous on March 8, 2000. Reviewed during March 23 teleconference.
3. March 16, 2000: Request for teleconference dated March 16, 2000, sent to Mr. Jack Purvis. Teleconference scheduled for March 28, 2000.
4. March 22, 2000: Agenda for March 23 teleconference, participant list, and synopsis of planned post-approval human mitoxantrone pharmacokinetic study, sent to Dr.'s Baweja and AlHabet. Complete, agreement reached on in vitro metabolism studies and human PK study. Minutes will be submitted to the NDA shortly.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 3819-6266.

Sincerely,

Mark W. Gauthier

APPEARS THIS WAY
ON ORIGINAL

51 University Street, Seattle, Washington 98101-2936
206.587.0430, Fax 206.587.0606 www.immunex.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Immunex Corporation	March 24, 2000
TELEPHONE NO. *(Include Area Code)* (206) 587-0430	FACSIMILE (FAX) Number *(Include Area Code)* (206) 223-0468
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 51 University Street Seattle, WA 98101 USA U.S. License #	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Immunex Corporation 51 University Street Seattle, WA 98101

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) License Number 1132

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mitoxantrone hydrochloride	Novantrone

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
	rhu GM-CSF

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	20mg,25mg,30mg(2mg/ml)	Intravenous

(PROPOSED) INDICATION(S) FOR USE:
Treatment for secondary - progressive multiple sclerosis

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Response to request for information

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 19-297,

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

TC A

immunex

Immunex Corporation
Regulatory Affairs
51 University Street
Seattle, WA 98101

Phone: 206 381-6266
Fax: 206 223-0468

FAX MESSAGE - PLEASE DELIVER IMMEDIATELY

Send to: Dr. Raman Baweja
Dr. Sayed AlHabet

Fax: (301) 480-3212

From: Mark W. Gauthier

Date: March 22, 2000

Total Number of Pages: 3 INCLUDING THIS PAGE

COMMENTS:

Dr.'s Baweja and AlHabet,

In preparation for the teleconference on Thursday March 23, I am providing a copy of our proposed post-approval study to capture the pharmacokinetic data requested in the approvable letter for NDA 21-120 dated March 1, 2000. We have previously provided copies of the protocols for the 4 in vitro metabolism studies also requested in the approvable letter and would like confirmation from you that the studies proposed are adequate to address your request. Listed below is our tentative agenda for the telecon and Immunex participants.

Agenda:
1. Confirm that proposed in vitro studies are appropriate and adequate to satisfy request.
2. Timing of studies - initiation, completion, availability of final report.
3. Acceptability of submitting in vitro metabolism data post-approval.
4. Review study protocol to address other post-approval commitments.
5. Follow up with Division of Neuropharmacological Drug Products – Dr. Baweja.

Immunex participants:
Mike Butine, Biometrics
Mark Gauthier, Regulatory Affairs
Mark Gilbert, Clinical Development
Mark Rogge, Pharmacokinetics and Clinical Toxicology
Richard Stead, Clinical Development
Dawn Viveash, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

We look forward to a productive teleconference with you.

If you have any comments or questions regarding this communication, please contact me at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Sr. Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859
Telecopier Cover Sheet

DATE:	**March 21, 2000**
TIME:	**12:05 PM**
DELIVER TO:	Mark Gauthier
Fax Number:	(206) 223-0468
Phone Number:	(206) 381-6266
FROM:	**Teresa Wheelous** 301-594-2850 Project Manager

APPEARS THIS WAY
ON ORIGINAL

Total number of pages, including cover page: 3

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:
Mark,

The following is a fax copy of the comments on NDA 19-297/S-022 from HFD-150 that should be incorporated into the response to NDA 21-120.

Teresa

APPEARS THIS WAY
ON ORIGINAL

immunex

Immunex Corporation
Regulatory Affairs
51 University Street
Seattle, WA 98101

Phone: 206 389-4066
Fax: 206 223-0468

FAX MESSAGE - PLEASE DELIVER IMMEDIATELY

Send to: Jack Purvis Fax: (301) 594-2858

From: Mark W. Gauthier Date: March 16, 2000

Total Number of Pages: 1 INCLUDING THIS PAGE

COMMENTS: **Re: NDA 21-120, Novantrone (mitoxantrone hydrochloride)**

Dear Mr. Purvis:

As we discussed earlier this morning, Immunex Corporation is requesting a teleconference with Dr. Katz and appropriate members of the Division to obtain clarification on several items in the March 1, 2000 approvable letter for NDA 21-120 and in the draft labeling provided with the letter. The points we wish to discuss are listed below. We anticipate that this should be a relatively short telecon and would like to schedule it as soon as possible (3/20 or 3/21).

1. We are tentatively planning to submit our response to the approvable letter the last week of March. We need to discuss the acceptability of sending a response that addresses all of the issues raised in the approvable letter with the exception of the in vitro metabolism data.
2. We have a telecon scheduled for March 23 with Dr.'s Baweja and AlHabet to discuss the pre and post approval pharmacokinetic requirements and timing of those responses. Dr. Baweja will obtain Dr. Katz concurrence on the outcome of those discussions.
3. Included in our responses will be a description of Immunex Corporation's concept for collection of post approval safety data, and a plan to ensure compliance with cardiac monitoring and cumulative dose restrictions. We would like to schedule a teleconference within one to two weeks after receipt of the package to obtain agreement on the plan.

If you have any questions, please call me at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Manager, Regulatory Affairs

File 31100, 31543

IMMUNEX

NA 3/22/00 DUPLICATE

NC

NEW CORRESP

March 8, 2000

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Woodmont II Building, 4th Floor
1451 Rockville Pike
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH

MAR 0 9 2000

RECEIVED HFD-120

RE: **NDA 21-120**
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Response to Approvable Letter

Dear Madam or Sir:

This letter serves as official notification of our intent to amend NDA 21-120 to address the questions outlined in the approvable letter dated March 1, 2000. The NDA requested approval of a new indication for Novantrone for the treatment of multiple sclerosis.

If you have additional comments or concerns regarding this submission, please contact me at your convenience at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Sr. Manager Regulatory Affairs

cc: Nancy Kercher

APPEARS THIS WAY
ON ORIGINAL

51 University Street, Seattle, Washington 98101-2936
206.587.0430, Fax 206.587.0606 www.immunex.com

. . would appreciate your review of the above protocols and confirmation that this will satisfy the Biopharmaceutics prior approval requirements for NDA 21-120. We would also appreciate your comments on the protocols per se.

If you have any questions regarding this submission, please call me at (206) 381-6266.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Mark W. Gauthier
Sr. Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD-120
Wheelous

Food and Drug Administration
Rockville MD 20857

Professor Giles Edan, M.D.
Centre Hospitalier Regional
Et Universitaire De Rennes
Pontchaillou - Rue Henri Le Guilloux
35033 Rennes Cedex
France

MAR 3 2000

Dear Dr. Edan:

Between November 2 and 5, 1999, Ms. Jeanne Diann Shaffer and Dr. Mathew T. Thomas, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (Protocol #31.0902) of the investigational drug mitoxantrone (Novantrone), performed for Lederle Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

We understand that your study was not conducted under a U.S. Investigational New Drug Application (IND), and that you did not know that your study would be submitted to FDA in support of drug claims. For future reference, we offer our comments so that you will recognize our requirements in clinical trials that you might conduct under a U.S. IND or ICH/GCP guidelines.

From our evaluation of the inspection report, the documents obtained during the inspection, and your written response dated November 19, 1999, regarding the findings itemized on the Form FDA 483, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, our personnel presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We emphasize the following:

1. You did not maintain adequate and accurate study drug accountability records in that you dispensed baseline study medications for 30 subjects although your records indicate that you received only 24 units of baseline study medications from the sponsor.

2. You did not maintain adequate and accurate study-related case-histories.

   a. A case report form (CRF) was not prepared and maintained for ——— who received baseline treatment and then dropped from the study.

   b. The -2 Month Visit (M-2) X-ray report and EKG tracing for subject #407 were not available during the inspection.

c. The Month 6 Visit (M6) EKG report for subject #410 was not available during the inspection.

We acknowledge your explanations and trust, as you stated, that corrective measures will be instituted to prevent similar problems in your current and future studies. Your letter dated November 19, 1999, and this letter will be included as a permanent part of your file. If information is requested from your file in accordance with the Freedom of Information Act, all relevant material will include all the related correspondences in your file; this will serve to give a more accurate and complete picture of this inspection.

We appreciate the cooperation shown our personnel during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301) 594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

MFD/OE
Reuzer-Kammayer

Food and Drug Administration
Rockville MD 20857

FEB 29 2000

Nicolaus König, M.D.
Medical Director
Marianne-Strauß-Klinik
Milchberg 21
82335 Berg-Kempfenhausen
Germany

Dear Dr. König:

Between November 8 and 11, 1999, Ms. Jeanne Diann Shaffer and Dr. Mathew T. Thomas, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (Protocol #31.0901) of the investigational drug mitoxantrone (Novantrone), performed for Immunex Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

We understand that your study was not conducted under a U.S. Investigational New Drug Application (IND), and that you did not know that your study would be submitted to FDA in support of drug claims. For future reference, we offer our comments so that you will recognize our requirements in clinical trials that you might conduct under a U.S. IND or ICH/GCP guidelines.

From our evaluation of the inspection report, the documents obtained during the inspection, and your written response dated November 25, 1999, regarding the findings itemized on the Form FDA 483, we conclude that you did not adhere to all pertinent regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, our personnel presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We emphasize that you did not report the adverse experiences of rib fractures and pneumothorax for subject #0113 and remind you that it is your responsibility to ensure that adverse experiences of subjects you enroll in the study are collected from all facilities where the subjects were seen during the study and accurately reported to the sponsor.

Your letter dated November 25, 1999, and this letter will be included as a permanent part of your file. If information is requested from your file in accordance with the Freedom of Information Act, all relevant material will include all the related correspondences in your file; this will serve to give a more complete picture.

We appreciate the cooperation shown our personnel during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301) 594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

that mitoxantrone at any approved dose can also cause myelosuppression should be added.

3. [redacted]

4. The applicant should delete the statement ' [redacted]

The statement "The extravasation site should be carefully monitored for signs of necrosis and/or phlebitis that may require further medical attention" should be added.

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/

Grant Williams, M.D.
Team Leader

cc:
NDA 19-297/SLR 022
HFD-150/Division files
HFD-150/Susan Honig
HFD-150/Alvis Dunson
HFD-120/T. Wheelous

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: February 29, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: NDA 21-120

SUBJECT: Supervisory Review of NDA 21-120, for the use of Novantrone to Treat Patients with Multiple Sclerosis

NDA 21-120 was submitted on 6/2/99 by Immunex Corporation, for the use of Novantrone (mitoxantrone) in patients with Multiple Sclerosis (MS). The sponsor's proposed Indication is "To slow progression of neurologic disability and reduce the relapse rate in patients with progressive multiple sclerosis". Novantrone is an anthracenedione that causes DNA strand breaks, interferes with RNA, and is a potent inhibitor of topoisomerase II. In the United States, it is approved for use in adults with Acute Non-Lymphocytic Leukemia, and for the treatment of pain in patients with symptomatic hormone refractory prostate cancer. It is approved in 50 countries as a treatment for various other cancers.

In this application, the sponsor has submitted the results of 2 randomized controlled trials that they believe establish the effectiveness of Novantrone as a treatment for patients with progressive MS. In addition, the application contains safety data for over 500 unique individuals with MS treated with at least one dose of Novantrone, as well as literature reports of safety experience in patients with various cancers.

The application has been reviewed by Dr. Janeth Rouzer-Kammeyer of the division (efficacy review dated 9/10/99), the safety data have been reviewed by Dr. Boehm of the Division (review dated 11/5/99), the statistical review of the effectiveness data was performed by Dr. Yan of the Division of Biometrics (review dated 11/26/99), and the pharmacokinetic data have been reviewed by Dr. Al-Habet of the Office of Clinical Pharmacology and Biopharmaceutics (review dated 11/10/99). Importantly, this application was presented to the Peripheral and Central Nervous Systems Drugs Advisory Committee at a public meeting on January 28, 2000. In this memo, I will briefly review the effectiveness and safety data, as well as the PCNS Advisory Committee's recommendations, and offer support for the Division's action on the NDA

EFFECTIVENESS

Study 031.0901

This was a randomized, placebo controlled, rater blinded, parallel group multi-center trial comparing the effects of 12 mg/m^2, 5 mg/m^2, and placebo in patients with secondary

progressive or remittent-progressive MS in an active phase of disease. Eligible patients were to receive treatment with study drug as an intravenous infusion every 3 months for 8 cycles, for a total study duration of 24 months. Patients were required to have an EDSS score of between 3 (able to walk unassisted) and 6 (needs assistance to walk). The EDSS is a standard scale used to assess function in patients with MS, and ranges from 0 (Normal neurological exam) to 10 (Death related to MS), with half-steps.

In this trial, the patients and treating neurologists were unblinded to treatment assignment, but an assessing neurologist at each center was blinded to treatment assignment. The diagnoses of relapse, and the decision to treat relapses with steroids were made by the unblinded physician.

The primary outcome in this study was a multi-variate test which combined results from the following 5 measures comparing the high dose to placebo:

1) Mean Change from Baseline in EDSS at 24 Months
2) Mean Change from Baseline in Ambulation Index (a commonly used 10 point scale ranging from 0-Normal to 9-Wheelchair, which measures increasing difficulty with ambulation)
3) Number of Relapses requiring steroid treatment
4) Time to First Relapse requiring steroid treatment
5) Mean Change from Baseline in Standardized Neurologic Status (a newly created scale which measures 5 functional groups: Definite Supraspinal Signs, Paresis, Spasticity, Sensation, and Bladder Impairment; each group has multiple sub-functions, each of which is given a numerical rating, the rating scale differing for each subfunction)

If the overall test was significant, each primary variable was to be tested in the following order: EDSS, AI, number of attacks, time to first attack, and SNS. Statistical testing was to be performed on an individual measure only if the preceding measure achieved statistical significance at p=0.05.

A number of secondary measures, all functions of the various primary measures, were also assessed. In addition, those patients enrolled at centers that had the capability, were assessed by gadolinium enhanced MRI and T2 weighted MRI.

Results

A total of 194 patients were enrolled at 17 centers in Germany, Belgium, Hungary, and Poland. The following chart (taken from the sponsor's Table 10.1.B, page 6 of Dr. Yan's review) displays the disposition of patients in the study:

	Placebo	Nov 5 mg/m2	Nov 12 mg/m2
Randomized	65	66	63
Completed	47 (72%)	54 (82%)	48 (76%)
Included in ITT Analysis	64 (98%)	64 (97%)	60 (95%)

For patients who did not complete the trial, the median time in study was 342 days for the placebo patients, 501 days for the low dose, and 385 days for the high dose group.

Half of the ITT population (N=94) were diagnosed with secondary progressive MS; half (N=94) with progressive relapsing MS. Approximately 45% of the placebo and high dose groups were diagnosed with progressive relapsing MS, while about 58% of the low dose group carried that diagnosis.

Patients were comparable on demographic measures at baseline. On average, patients had had about 1.3 relapses in the 12 months prior to study entry, and deteriorated about 1.5-1.6 points on the EDSS over the 18 months prior to enrollment.

APPEARS THIS WAY
ON ORIGINAL

The following table displays the results for the individual outcome measures:

Test	Baseline			Change at 24 Months			P-value vs Pla	
	Pla	5 mg/m^2	12 mg/m^2	Pla	5 mg/m^2	12 mg/m^2	5 m/m^2	12 m/m^2
EDSS	4.69	4.64	4.45	0.23	-0.23	-0.13	0.0098	0.0194
AI	2.63	2.52	2.52	0.77	0.41	0.30	0.0560	0.0306
#Relapses Treated				76.8	46.9	24.1	0.0293	0.0002
Time to First Treated Relapse Median (Months)				14.2	NR	NR	0.0549	0.0004
SNS	20.94	18.88	19.33	0.77	-0.38	-1.07	0.2912	0.0269

The overall difference between the 12 mg/m2 group and the placebo group was 0.3094, a number that has no easily understood clinical meaning; the p-value for the overall test was 0.0001. As Dr. Yan notes, however (Page 17), neither the sponsor nor she have a detailed understanding of the software used to run this analysis.

MRI

As noted above, MRIs were performed at a subset of the centers in the trial. Results were read blinded independently by 2 experts who then reached a consensus on each scan. The following subset of patients received MRI scans at Baseline, 12 months, and 24 months:

	N
Placebo	36 (56%)
Nov 5 mg/m^2	40 (63%)
Nov 12 mg/m^2	34 (57%)

The following results were seen:

Measure	Placebo			N 5mg/m^2			N 12 mg/m^2		
	Base	M12	M24	Base	M12	M24	Base	M12	M24
# of Pts with Gd + lesions	8	7	5	19	6	4	10	5	1
# of Pts with new Gd+ lesions		7	5		6	4		4	0

Measure	Placebo			N 5mg/m^2			N 12 mg/m^2		
	Base	M12	M24	Base	M12	M24	Base	M12	M24
Mean # of Gd+ lesion	0.44	0.31	0.28	3.23	0.30	0.11	1.88	0.15	0.03
Mean Change From Base In # of Gd+ lesions		-0.14	-0.19		-2.93	-3.27		-1.74	-2.03
P-value for Mean Change From Baseline						0.0031			0.095

Study 031.0902

This was a multi-center, parallel group, open, parallel group controlled trial in patients designed to evaluate the effectiveness of Novantrone in patients with "severe" MS. In this study, patients with severe (defined as those patients who had a current risk of presenting a major handicap) and active (based on having had at least 2 attacks in the year prior to enrollment or progression characterized as an increase in Kurtzke score of at least 2 points after an attack- i.e., secondary progressive MS) disease were randomized to receive either Novantrone 20 mg plus methylprednisolone or methylprednisolone alone, given intravenously once a month for 6 months. Neither the patient nor the treating neurologist was blind to treatment assignment.

The primary outcome measure in this study was the percentage of change from baseline in the number of patients without active lesions on MRI at each month of the study. An active lesion was defined as a new lesion (not present at baseline), a lesion present at baseline that increased in size, or Gd enhancement. The protocol did not state (nor did

the study report) if lesions that were Gd+ at baseline and were still Gd+ during treatment (but that did not increase in size) were to be considered active lesions.

All MRIs were read by a single blinded expert reviewer.

Eligible patients entered a 2 month pre-randomization period, during which they were scanned at Month –2, Month –1, and Month 0. The Month –1 and Month 0 scans were each taken 1 month after an intravenous dose of 1 gm of methylprednisolone. Patients who developed at least 1 new Gd+ lesion during this period of time were randomized after the Month 0 scan.

Results

A total of 42 patients (21 in each group) were randomized at 5 centers in France. A total of 5 patients withdrew after treatment initiation; all in the control group, all due to marked deterioration in disease.

Of the 21 Novantrone treated patients, 15 (71%) had relapsing-remitting MS, while 6 (29%) had secondary progressive MS. Of the control patients, 17 (81%) had relapsing-remitting MS, while 19% had secondary progressive disease.

Patients were comparable at baseline in demographic measures. On average, patients had had MS for about 6 years prior to enrollment, with an average of about 2-3 relapses in the year prior to enrollment.

The following chart, taken from sponsor's Table 6.1.1 (reprinted in Dr. Yan's review, page 26), displays the results, by month, of the primary measure, the number of patients without active lesions, as previously defined:

Month	Novantrone	Control	P-value
M-1	3/20 (15%)	3/20 (15%)	1.000
M0	2/20 (10%)	1/21 (5%)	0.606
M1	3/21 (14%)	4/21 (19%)	1.000
M2	11/21 (52%)	3/21 (14%)	0.009
M3	13/21 (62%)	6/21 (29%)	0.030
M4	13/21 (62%)	7/20 (35%)	0.085
M5	14/21 (67%)	5/16 (31%)	0.033
M6	19/21 (90%)	5/16 (31%)	0.001

The primary measure was the percent change in the number of patients without active lesions at Month 6 compared to Baseline (defined as Month-2). This was significant with p=0.011.

The following chart, taken from sponsor's Table 6.1.2.A (Dr. Yan's review, page 27) displays the results of the Mean Number of New Gd+ Lesions:

Month	Novantrone	Control	P-value
M-1	6.8	9.1	NS
M0	4.6	5.1	NS
M1	1.9	12.3	0.036
M2	2.6	5.7	0.017
M3	1.1	9.2	0.011
M4	0.9	8.9	0.035
M5	0.6	3.8	0.009
M6	0.1	2.9	0.001

APPEARS THIS WAY ON ORIGINAL

The sponsor also evaluated EDSS in this study; the following chart, taken from sponsor's Table 6.2.1.A (Dr. Yan's review, page 28) displays the results of the analyses of the Mean Change from Baseline (defined as Month 0) by month:

Month	Novantrone		Control		P-value
	Mean EDSS	Change	Mean EDSS	Change	
M0	4.5	---	4.6	----	
M1	4.2	-0.3	4.9	0.2	NS
M2	4.1	-0.4	4.9	0.3	0.024
M3	3.9	-0.6	5.0	0.3	0.008
M4	3.6	-0.9	5.1	0.6	0.001
M5	3.4	-1.1	4.5	0.1	0.002
M6	3.4	-1.1	4.3	-0.1	0.013

SAFETY

The NDA contains safety information from several datasources; because Novantrone has been approved in the US since 1987 for the treatment of Acute Non-Lymphocytic Leukemia, and since 1996 for the treatment of pain in patients with hormone resistant prostate cancer, Dr. Boehm has reviewed data from our Post-Marketing reports for certain selected adverse events, and the sponsor has provided some information from Novantrone's use in patients with various cancers. In addition, of course, the sponsor has submitted detailed safety data from the 2 controlled trials discussed above, as well as from a cohort of patients treated over a number of years in an MS clinic in Germany. Because the dosing regimens and durations of treatment used in the 2 controlled trials are quite distinct, I will describe the safety experience from these 2 trials separately. In addition, because the German experience was open and uncontrolled, I will describe that separately as well.

Exposure

Experience in a total of 599 unique patients with MS receiving at least one dose of Novantrone is described in the NDA (Study 31.0901, N=124; Study 31.0902, N=21; German Study, N=454). While the data from the 2 controlled trials was documented in a prospective manner, the German experience represents all the patients treated in this clinic over a 10 year period (1988-1998), the data from which was extracted onto case report forms (CRFs) retrospectively. Patients in this latter cohort were not monitored in as formal a way as those in the controlled trials, and follow-up for these patients was less complete. Most patients in the German cohort were treated with 12 mg/m^2 every 3 months.

Study 31.0901

Exposure –

A total of 122 patients received Novantrone for at least 6 months in this trial, and 111 received drug for 1 year. The mean cumulative dose was about 83 mg/m^2 in the high dose group and 37 mg/m^2 in the low dose group. The highest cumulative dose achieved in this study was 96 mg/m^2, which corresponds to the dose achieved if all doses in the high dose group were given.

Deaths

No deaths were reported during this trial. There were no deaths reported up to 12 months after the last dose, although complete follow-up was unavailable for 11 patients.

Discontinuations

A total of 17/64 placebo patients (27%) discontinued, compared to 10/64 low dose patients (16%) and 12/60 (20%) of high dose patients. A total of 2 (3%) of placebo and 5 (8%) of high dose patients discontinued due to adverse events. Of the 5 Novantrone patients discontinuing for adverse events, 1 had depression and suicidal ideation, 1 had left ventricular fractional shortening of 22% (baseline 41%, lower limit of normal 25%) after 4 doses which returned to 33% 1 year after discontinuation, 1 had persistent nausea and vomiting, one had a creatinine of 4.7 mg/dL associated with urinary retention and hydronephrosis which improved after catheterization of the bladder, and 1 had repeated UTIs.

Serious Adverse Events

The sponsor reported 10 serious AEs in each treated group (16% and 17% in low and high dose groups, respectively) and 6 (9%) in the placebo group.

In the high dose group, SAEs of interest not already discussed above included 2 cases of necrosis of the femoral head (both patients had previously received treatment with corticosteroids), hemorrhagic cystitis, which occurred after the first dose and did not recur with dose decrease, and endometritis.

Other Adverse Events

Over 85% of all patients in this trial reported at least one treatment emergent adverse event. The following table, taken from the sponsor's Table 12.1.2.A, reproduced in Dr. Boehm's review (page 13) lists those AEs that occurred in at least 5% of the high dose patients and for which the incidence was at least twice that of the placebo patients:

Event	Placebo (%)	Low Dose (%)	High Dose (%)
Nausea	20	55	76
Alopecia	31	38	61
UTI	13	29	32
Menstrual Disorder	26	51	61
Stomatitis	8	15	19
Amenorrhea	3	28	43
Leukopenia	0	9	19
Arrythmia	8	6	18
Gamma GT Increased	3	3	15
EKG abn'l	3	5	11
Sinusitis	2	3	6
Granulocyto-Penia	2	6	6
WBC abn'l	2	8	6
Anemia	2	9	6

There was a dose response for cardiac adverse events, with 9% of placebo patients, 6% of low dose, and 21% of high dose patients reported as having had a cardiac adverse event; most of this difference was related to events coded as arrhythmia. In addition, about 3% of placebo patients, 5% of low dose patients, and 11% of high dose patients were reported as having had an abnormal EKG. There was no further description of the nature of either the arrhythmias or abnormal EKGs reported.

Although about 86%, 77%, and 75% of patients randomized to low dose, high dose, and placebo, respectively, received all 8 courses of therapy, about 45% (N=27) of high dose and 9% (N=6) of low dose patients had their doses reduced secondary to adverse events. A total of 9 patients had their dose reduced because of hematologic toxicity (all in the

high dose group), and 6 low dose and 22 high dose patients had their doses reduced secondary to non-hematologic toxicity; there are no further details about the nature of these toxicities.

Laboratory measurements were made at baseline and prior to each treatment course. Given this schedule of monitoring, it was impossible to characterize the true time course of any lab abnormalities.

Examination of the change from baseline in mean values for hematologic parameters revealed a dose related mean decrease in platelet count at 1 year and at study end, and examination of the proportion of outliers on these measures shows a dose related increase in the proportion of patients who met outlier criteria for platelet and WBC count as described below (taken from Dr. Boehm's table on page 16 of his review):

	Placebo	Low Dose	High Dose
WBC	7%	22%	37%
Platelets	5%	8%	11%

A total of 11 patients in the high dose, 4 patients in the low dose, and 2 patients in the placebo groups had neutrophil counts below $2x10^9$/L at any time. No patient had a neutrophil count below $0.5x10^9$/L. Two patients (1 each in the low dose and placebo groups) had platelet counts below 100,000/cu mm.

Examination of the results of liver function testing revealed a very minor dose response in mean SGOT level, with a dose related increase in the proportion of patients who met outlier criteria for SGOT elevation as seen below (taken from Dr. Boehm's table, page 18 of his review):

	Placebo	Low Dose	High Dose
SGOT	15%	27%	30%

Further examination of these patients revealed no important differences across groups in the proportion of patients who had an SGOT>100U/L.

A total of 3%, 6%, and 8% of placebo, low dose, and high dose patients, respectively, had ejection fractions (assessed by echocardiography) at 24 months that were at least 10% lower than baseline levels. A total of 1(1.7%), 2(3.3%), and 3 (5.5%) of placebo, low dose, and high dose patients, respectively, had ejection fractions of less than 50% of their baseline levels. There are no details provided about the patients' clinical status. As noted earlier, one subject (high dose) discontinued for a decrease in ejection fraction.

Although the sponsor did not provide complete follow-up at 36 months for all patients, 4 patients (3 low dose, 1 high dose) who had normal EFs at 24 months had further decreases at 36 months, as seen below (Dr. Boehm's table, page 19 of his review):

Patient	Dose	24 mth EF	36 mth EF
501	5	80%	53%
5302	5	61%	58%
5401	5	56%	45%
408	12	57%	40%

APPEARS THIS WAY ON ORIGINAL

Study 31.0902

Exposure

The mean cumulative dose in this study was about 81 mg/m^2, with a range of 62-101 mg/m^2 (recall that patients in this study received 20 mg once a month for 6 months).

Deaths

There were no deaths during this study.

Discontinuations

One patient in the Novantrone group was discontinued after the first dose due to elevated LFTs, which were attributed to fluoxetine. A total of 6 control patients discontinued treatment, all related to disease progression.

Serious Adverse Events

No SAEs were reported in this study.

Other Adverse Events

The following table, adapted from Sponsor's Table F.5.7., reproduced in Dr. Boehm's review, page 21, lists adverse events that occurred in greater than 5% (N>1) of Novantrone treated patients, and more than twice as frequently as in the control (methylprednisolone) group:

Event	Novantrone (%)	Control (%)
Amenorrhea	8 (53)	0
Alopecia	7 (33)	0
Nausea	6 (29)	0
Asthenia	5 (24)	0

APPEARS THIS WAY ON ORIGINAL

Event	Novantrone (%)	Control (%)
UTI	4 (14)	1 (5)
Throat Infection	3 (14)	1 (5)
Gastralgia	2 (10)	0
Pharyngitis	2 (10)	0
Rhinitis	2 (10)	0
Mycosis	2 (10)	0
Aphthosis	2 (10)	0
Epigastric Pain	2 (10)	1 (5)

Lab Testing

Hematology

Hematologic monitoring was performed every week for the Novantrone patients and every month for control patients.

Novantrone treated patients experienced slightly greater differences than controls in mean difference from Baseline at Month 6 in hemoglobin, WBC, neutrophils, and platelets. A total of 48% of Novantrone patients (10/21) had a WBC count below $2.0x10^9$/L, and none had a count below $1x10^9$/L at any time. A total of 19 Novantrone patients (90%) had a neutrophil count of less than or equal to $1x10^9$/L at least once during the trial, and 9 (43%) had at least one neutrophil count below $0.5x10^9$/L during the trial. All but 3 of these latter patients had neutrophil counts greater than $0.5x10^9$/L at the next measurement one week later. No subject (although there were some missing values) had neutrophil counts less than $0.5x10^9$/L by week 4 of any month of treatment.

Dr. Boehm has examined the risk of experiencing low neutrophil counts over time in the Novantrone treated patients (see his table, page 23 of his review). He has found that the risk of experiencing such events persists and/or increases over time. For example, displayed below are the risks for developing these abnormalities at Month 1 and Month 6:

Month	% with Count<$1x10^9$/L	% with Count<$0.5x10^9$/L
1	48%	10%
6	57%	29%

No Novantrone treated patients experienced a platelet count below 100,000/cu mm.

Other laboratory measurements were evaluated on a monthly basis. Novantrone treated patients had slightly greater mean increases (Month 6 compared to Month 0) in creatinine, AST, and alk phos compared to controls. There were no important differences

between drug and control patients in the proportion of patients reaching outlier criteria for any lab measurement.

There was a slight increase in the number of Novantrone treated patients who met outlier criteria for decreased systolic and diastolic blood pressure and decreased hear rate at any time during the trial compared to the control treated patients, but the absolute systolic or diastolic pressures were not dangerously low.

Cardiac function was assessed at baseline and at Month 6 by EKG and echocardiogram. There were no important between treatment differences as measured by these assays.

German Cohort

As noted above, the sponsor identified a total of 454 patients treated at an academic referral center in Germany over the 10 year period 1988-1998. Data from the medical charts were transcribed onto a Case Report Form (CRF), but the sponsor did not have access to the original records. The occurrence of certain adverse events (e.g., cardiotoxicity, malignancies, treatment with antibiotics) was noted, but severity information was not collected. The following laboratory tests were recorded on the CRFs: leukocyte count, lymphocyte count, granulocyte counts, and immunoglobulin concentrations.

The standard dose in these patients was 12 mg/m^2 every 3 months. The mean number of doses received in this cohort was 4.4. A total of 85% of the patients received at least 2 doses, with 64% receiving at least 8 doses. The mean dose was 9.8 mg/m^2, and the mean cumulative dose was about 44 mg/m^2. A total of 93% of patients (424/454) received a cumulative dose of less than 100 mg/m^2, with the greatest cumulative dose being about 183 mg/m^2. The mean number of months of follow-up was about 47 months, with the longest duration of follow-up being about 121 months.

Deaths

There were a total of 20 deaths in this cohort. A total of 11 patients died greater than 3 years after their last dose and 3 died within 19 months of their last dose. A total of 8 deaths were attributed to pneumonia and 5 to insufficiency of breath, the cause of death was unknown for 3 patients, and the remaining 4 were attributed to bladder dysfunction/infections, cachexia, heart failure, and pulmonary infection + cardiomyopathia.

Discontinuations

According to the sponsor, 341 patients discontinued treatment; the other 113 were continuing to receive treatment at the time of the submission.

Of the 341 who discontinued, apparently 77 discontinued because they were treatment successes, and 44 discontinued because they were treatment failures. Dr. Boehm

identified 32 patients who discontinued for adverse events (34 according to the sponsor), and 147 discontinued for Other reasons (not further specified, though most were listed as patient refusals), and the reasons were unknown for 4 patients and not completed for 15 other patients.

Of the 32 identified by Dr. Boehm as having discontinued for adverse events, 9 were for leukopenia, 5 were for lymphopenia, 5 were for cardiac events, 3 were for infection, 3 were for vomiting, and 1 each for weakness, reduced condition, increased liver enzymes, hepatitis C, very bad condition, skin necrosis, and no reason given. Dr. Boehm identified 7 patients whose reason for discontinuing treatment was given as "patient refusal" for whom the discontinuation appeared to have been associated with an adverse event (2 decreased leukocytes, 2 vomiting, 1 each alopecia, infection, decreased EF), and 4 whose reason for discontinuation was given as "treatment failure" in whom an adverse event appeared implicated (leukopenia, lymphopenia, infection, and alopecia).

No narrative descriptions of these events were included in the submission.

Serious Adverse Events

The sponsor asserts that there were no serious AEs reported.

Other Adverse Events

As noted above, information was collected about only a limited number of adverse events.

The sponsor reported that 38% of patients experienced an infection, 86% of which were called UTIs, and 12% of which were of unknown type. Few other additional details are available.

The sponsor reports that patients were examined with echocardiograms to assess clinical findings suggestive of cardiac toxicity and in those with a cumulative dose of at least 140 mg/m^2 before each treatment course. A total of 45% (203/454) had at least 1 echocardiogram and only 6 of these had a cumulative dose of at least 140 mg/m^2; therefore, as noted by Dr. Boehm, most of these patients were monitored for reasons that are not clear. Of the 203 patients in whom an echocardiogram was performed, 43 (21%) had an abnormality. These included ventricular dilation/dysfunction, pericardial effusion, and valvular abnormalities. Severity of these events was not recorded.

EKGs were routinely performed before each treatment course, and all but 1 patient had at least 1 EKG; the mean number/patient was 4.3. A total of 32% (143/453) had at least one abnormality, the most common being conduction block in 17% of patients. A total of 2% had ventricular hypertrophy.

According to the sponsor, 7 patients developed cardiac toxicity. The cumulative dose in these patients ranged from about 41 to 130 mg/m^2. Details were presented only for those

patients who died. One was a 42 year old man treated with a cumulative dose of 91 mg/m^2 at the clinic between 1990-92. He then received an additional 120 mg between 1994-96 from his doctor. Two months after the last dose, he died in cardiogenic shock.

The second case was a 41 year old man who received a cumulative dose of 50 mg/m^2 at which time an echo showed diffuse hypokinesia of the left ventricle with a reduction of EF at rest. The drug was stopped, and the patient died during the next year (?date), with the death attributed to respiratory insufficiency during a URI.

A total of 12% of women reported amenorrhea, with 27% of these women recovering after therapy was discontinued. Information about the duration of treatment in the women who did not recover was not submitted in the application.

Lab tests

Hematology assessments were made prior to each treatment course. A total of 28 patients (6%) had WBC less than 2000/ cu mm, but none had a WBC below 1000/cu mm. A total of 62 patients (14%) had neutrophil counts between 500 and 1000/cu mm, with 12 patients having a neutrophil count below 500/cu mm. No additional data about these patients was submitted.

Post-Marketing Reports

Dr. Boehm has concentrated his examination on a subset of the 598 spontaneous reports of adverse events submitted to the Agency's database. This subset consists of reports of rhabdomyolosis, renal or hepatic failure, and congestive heart failure.

There were 2 reports of elevated CPK, both of which occurred in the context of an MI. There was a single report of a 46 year old woman with rhabdomyolosis and renal failure after a single course of Novantrone and cyclophosphamide.

There were 5 reports of liver failure, 4 of which occurred in the context of multi-organ failure. The remaining case was a 15 year old female treated with Ara-C and Novantrone for AML. She developed slightly elevated ALT and AST 2 weeks after the first treatment course, after which she received a second (reduced) dose after the enzymes had normalized. About a month later, she was jaundiced (bilirubin 2.6 mg%) and had LFTs between 3-4000U/L. She died with massive hepatic necrosis observed on autopsy.

A total of 15 reports of renal failure occur in the Agency's post-marketing database, none of which seemed to be a primary event. A number of the cases occurred in patients receiving other nephrotoxic drugs, in the setting of multi-organ failure, or the cases were inadequately described.

Cardiac Toxicity

There was a single case reported of cardiac toxicity in an MS patient. This was a 32 year old woman (treated in Belgium) who developed massive, refractory cardiac failure 2 months after her last dose of Novantrone. She had received a cumulative dose of about 170-180 mg/m^2 over an unknown duration. She had been receiving concomitant lithium, and she died.

Dr. Boehm identified 56 reports of cardiac toxicity (decreased EF or CHF) in patients without a reported MI. Many of these patients had previously received anthracyclines or radiation to the chest, which are accepted as risk factors for the development of cardiac toxicity in patients treated with Novantrone. Dr. Boehm investigated these cases for patients who experienced cardiac toxicity with relatively low cumulative doses of Novantrone, and identified at least 4 such cases (previous exposure to identified risk factors unknown). These cases ranged from markedly decreased EF to cardiac failure (1 death) at doses as low as 10 mg/m^2.

Literature Reports

Dr. Boehm has reviewed several articles from the published literature that examine the risk of cardiac failure with Novantrone treatment in several large cohorts of cancer patients. His detailed discussion of this issue can be found on pages 32-34 of his review; I will very briefly describe below the conclusions reached by the authors of these articles. It is important to note that the number of patients receiving the highest doses in all of these cohorts was small.

One article examined the cumulative risk of CHF in a cohort of 1228 patients. This article describes a cumulative risk of CHF of about 2% up to a cumulative dose of about 120 mg/m^2 in patients not previously treated with an anthracycline. In this cohort, a cumulative dose of greater than 160 mg/m^2 was associated with a steep increase in risk for CHF.

A second article, describing the experience in 774 patients, also revealed a cumulative risk of CHF of about 1-2% up to a dose of 160 mg/m^2 in patients not previously treated with doxorubicin, after which the risk of CHF rose sharply.

A third article, describing the experience of 1211 patients again documented a cumulative risk of CHF of about 2% up to a cumulative dose of 120 mg/m^2, after which the risk rose sharply above a dose of 160 mg/m^2.

A fourth article also described an increase in risk for cardiac toxicity by dose and duration in a cohort of 801 cancer patients.

Other reports in the literature describe cardiac toxicity in cancer patients treated with Novantrone, but do not examine the relationship between cumulative dose and risk.

The sponsor identified 8 literature reports of Novantrone experience in MS patients. Most of these articles describe small numbers of patients treated, and are either silent on risk for CHF, or identify no cardiac toxicity (many do not describe the method of monitoring for these effects).

The largest MS experience reported in the literature, (Gonsett RE, Mitoxantrone Immunotherapy in Multiple Sclerosis, Multiple Sclerosis, 1, 329-332, 1996) describes the treatment of 68 patients. About 12% of patients developed cardiac toxicity (mostly described as decreased EF); the range of cumulative doses was 94-207 mg/m^2. One patient, who received the highest dose, died of heart failure 2 months after her last dose.

Other toxicities known to be associated with Novantrone treatment

Leukemia

It is believed that topoisomerase II inhibitors, including Novantrone, when used in combination with other antineoplastics, are associated with the development of acute leukemia.

According to the sponsor, 2 different types of leukemia may occur. The first is associated with a relatively long latency (3-5 years), has a pre-leukemic phase, and has a poor prognosis. The second type has a relatively short latency (<3 years), a myelocytic or monocytic predominance, and a relatively good prognosis.

As described by Dr. Boehm (page 36 of his review), the sponsor has reviewed 6 publications describing the risk of leukemia in patients treated with Novantrone. These patients were all treated with concomitant antineoplastics, and the risk of leukemia varied from 0.3% to 5%, with latencies ranging from 1.5-6 years. There were no such malignancies seen in the NDA database, although the sponsor describes a case report of an MS patient who received a cumulative Novantrone dose of 87.5 mg/m^2 and developed leukemia 5 years after the last dose.

QUESTIONS

- The sponsor has presented the results of 2 randomized controlled trials that they believe establish the effectiveness of Novantrone as a treatment that slows the progression of neurologic disability and reduces the relapse rate in patients with progressive multiple sclerosis. In addition, the sponsor concludes that the safety data generated in MS patients, as well as the safety experience gained in patients with other diagnoses, supports the approval of the application.

The application poses a number of interesting issues.

1. Has the sponsor submitted substantial evidence of effectiveness to support a claim for patients with Progressive Multiple Sclerosis?

In Study 0901, patients with secondary progressive or remittent progressive MS were enrolled. In Study 0902, while the inclusion criteria required that patients have active MS, the vast majority of patients enrolled were diagnosed with relapsing-remitting MS, not progressive MS. Given this, it is fair to ask if the data presented constitute substantial evidence of effectiveness (ordinarily defined as data from at least 2 independent experiments) for any claim in patients with progressive MS.

This issue was discussed at great length at the PCNS meeting of 1/28/00. Dr. Fred Lublin, a recognized expert from Hahnemann Medical College in Philadelphia, presented the current categorization of MS types on behalf of the sponsor. Dr. Lublin noted that current nosology recognizes 2 sub-types of relapsing-remitting MS. In the first type, patients return to an essentially normal baseline between relapses; in the second type, patients do not return to a normal baseline between relapses. In this second type, while a patient's status is not normal between relapses, there is no progression during this inter-relapse interval (this distinguishes this type of MS from relapsing-progressive, in which patients are seen to progress during the period between relapses). Dr. Lublin acknowledged that the patients in Study 902 appeared, for the most part, to have relapsing-remitting MS, but of the second type. The Committee agreed that these patients appeared to have this more aggressive form of relapsing-remitting MS, based largely on the average EDSS at baseline in these patients (the baseline EDSS was about 4.5, indicating that these patients were not normal in between relapses). For this reason, the Committee agreed that the sponsor had submitted 2 trials that had examined patients with either progressive or worsening MS.

2. Has the sponsor submitted substantial evidence of effectiveness to support a claim for an effect on progression of neurologic disability? For an effect on relapse rate?

The Division has been reluctant to grant a claim for the slowing of progression of any degenerative neurologic illness in the absence of a controlled trial that is designed to demonstrate such an effect. Specifically, such a trial would incorporate some variant of a design in which patients originally randomized to active treatment are withdrawn from treatment and whose subsequent course is compared to that of patients originally randomized to, and continuing on, placebo. If the difference in treatment effect seen between active treatment and placebo persists when the active patients are withdrawn from treatment, this would imply an effect on the underlying progression of the disease. In the absence of some design that incorporates such features, any effect seen on, for example, a scale that ostensibly measures function (as the EDSS does in this trial), may simply reflect a symptomatic effect.

In this case, though, an additional factor, namely the existence of MRI data, is present.

Of course, the primary outcome of Study 0902 was the Percentage of Patients Without New Gd-Enhanced Lesions, an MRI measure, which was highly statistically significant.

Again, the Division has been reluctant to base a conclusion about the effectiveness of a product on a measure other than a measure of direct clinical benefit (e.g., a relevant scale measuring functionality, a counting of relevant clinical events, etc). Indeed, I am aware of no instance in which the Division has considered a controlled trial "positive" on the basis of such a measure. This is not the say that the Agency has not done so; such measures are routinely used in some clinical settings, and, specifically, the approval of Betaseron was based, in part, on its effects on MRI.

The use of an MRI measure on which to base a finding of effectiveness raises the important question of the appropriateness of the use of surrogate markers in this setting.

The Agency has incorporated in its regulations (Subpart H of the NDA regulations, so-called Accelerated Approval), and more recently in the Federal Food, Drug, and Cosmetic Act (since 1997), provisions for basing a finding of substantial evidence on controlled trials in which a treatment demonstrates an effect on a surrogate marker (a laboratory or other measure that is not a direct clinical measure). In the absence of true validation of the surrogate (validation would imply that an effect on the surrogate is known to reliably predict the clinical effect of interest), an effect on such a measure must be reasonably likely to predict the drug's effect on the clinical outcome of interest. Reliance on a drug's effect on an unvalidated surrogate as being reasonably likely tc predict a future clinical effect is almost always problematic and raises several important questions (it is worth noting that there appears to be general agreement that MRI in patients with MS has not been validated as a surrogate in the sense I have been talking about).

The first issue that must be addressed is whether or not the treatment interferes with the measurement itself. That is, does the treatment interact with the assay system so that the surrogate itself is altered (in this case, for example, is there an interaction between Novantrone and the injected Gadolinium) with no concomitant change in the brain? Then, it is reasonable to ask if there are effects on the brain that are reflected in the surrogate, but that are of no clinical consequence. For example, if generalized atrophy is taken as an MRI surrogate, it is possible to imagine that a treatment may increase brain water, so that the brain may no longer appear atrophic, but such an effect would be of no clinical utility.

This latter may be an example of a more general potential problem with surrogates; that is, the factors influencing the surrogate may not be in the "direct pathway" of the pathophysiologic events giving rise to the disease state; in such a case, the drug may have a "beneficial" effect on the surrogate, but no effect at all on the disease to be treated. In addition, the drug may have an unintended effect on the disease as well as the desired effect on the surrogate, so that the condition may actually be worsened in the face of a "beneficial" effect on the surrogate (some see this more as a safety issue, rather than as a failure of the surrogate, but, in either case, the effect on the surrogate may be misleading). Further, the effect on the surrogate may be short-lived, such that the any

effect seen will not be reflected in the predicted long term effect desired on the clinical outcome of interest.

The sponsor's use of the MRI findings, however, while raising the question of its use as a surrogate as defined in the regulations (that is, to predict future clinical benefit), also raises the question of its use as what can be called a contemporaneous surrogate. By this, I mean the use of this specific MRI measure as a reflection of the underlying brain pathology at the time of the scan. When used as this type of surrogate, the claim would be that an effect on the MRI accurately reflects the drug's effect on the underlying brain pathology at that time. In this formulation, the case could be made that a beneficial effect on the surrogate is reflected in an effect on the underlying pathology which could be considered, by definition, beneficial for the patient, even in the absence of a manifest clinical benefit (for example, the lesions seen may be in "silent" brain areas, clinical measures are too insensitive to detect such changes, etc).

When used in this way, though, additional questions are raised.

The first question we can ask is what specific MRI measure reflects what specific brain pathology (and, in particular here, what pathology is reflected in the specific MRI measures used in this study, and what is the evidence for the answer given).

We must further ask if the effect on the surrogate is so small that it can never be reflected in any meaningful clinical benefit (after all, any use of a surrogate must be based on the presumption that it reflects some benefit to the patient). For example, suppose the effect on the MRI reflects the preservation of a very small number of neurons (given its great sensitivity); it is possible that such an effect could never be reflected in a meaningful clinical benefit, regardless of how sensitive such measures could be made. In the typical case, when clinical measures are used as primary outcomes, we are usually not concerned about the size of the treatment effect seen; we accept, ordinarily, that any effect shown to be statistically significant is worthwhile from a clinical point of view (it establishes proof of principle of the effect of the treatment). Use of a surrogate, however, requires that we consider the size of the effect. This is problematic, because if the clinical effect associated with a particular effect on the surrogate is trivial (or non-existent), and we do not know how to establish this clinical effect, it is difficult to make a risk-benefit decision about the drug.

It should be noted that there is general agreement by MS experts that MRI (at least some measures) accurately reflects underlying brain pathology, and many such experts believe that MRI should be accepted as an adequate surrogate on which to base a decision about the effectiveness of a drug.

There was considerable discussion on this point at the PCNS meeting. There was, I believe, general agreement that the study was not adequately designed to address the question, but that the MRI data was consistent with an effect on at least some aspects of the underlying pathology of the treatment (specifically inflammation) at least while the treatment was being given (that is, the Committee felt that the data do not speak to the

question of whether or not the treatment could slow the ultimate progression of the disease in the predictive sense). The Committee did not come to complete agreement on the specific claim that could be granted on the basis of this data, but it was clear that they felt that some language that communicated an effect on the underlying pathology would be warranted.

Also, any putative effect on relapse rate needs to be examined.

In this context, it is critical to recall that these trials were unblinded. Study 0901 utilized a blinded evaluator, while Study 0902 did not (for the clinical outcomes). Recall that in Study 0901, the primary outcome was a combination of 5 measures. Three of these measures were functional scales and 2 measures were related to relapse, Time to First Relapse Treated with Steroids, and the Number of such relapses, and while the between treatment comparison for all of these measures reached statistical significance, the diagnosis of a relapse, and the decision to treat a relapse with steroids were made by the unblinded treating physician, and the diagnoses of relapses in Study 0902 were made by neurologists who were aware of the treatment assignments as well, as were the patients. In both trials, then, the diagnoses and decisions to treat relapses were made by unblinded observers.

Again, the Committee discussed this issue in depth. There was again general agreement that, while the fact of unblinding on this important measure was less than ideal, the sponsor had submitted substantial evidence of effectiveness for an effect on relapse rate. In this regard, the Committee was particularly impressed by the sponsor's contention that the vast majority of the relapses were considered "severe", and that, therefore, their diagnosis was not terribly susceptible to blind breaking. The sponsor noted that there were several criteria included in the protocols for characterizing relapses as severe, and that most of the relapses met one of these criteria. One criterion required an increase in EDSS during the relapse of at least 2 points, while a second criterion required an increase of at least one point on one of a number of functional groups on an unnamed scale. The sponsor could not state, however, which of the relapses met which criteria, nor did they seem to have detailed information about the clinical characteristics of any of the individual relapses.

3. What is the effective dose?

The two controlled trials used markedly different dosing regimens, and the appropriate regimen to be recommended in labeling is not immediately obvious. Ordinarily, the Agency might not require that a particular dosing regimen be shown to be an effective regimen in 2 independent trials; however, in this case, given the potential serious risks (see below), it is worth discussing whether or not the sponsor has submitted sufficient evidence to justify a specific dosing recommendation.

The Committee considered this question as well, and concluded that the high dose regimen used in Study 001 (12 mg/m2 every 3 months) would be the appropriate regimen to recommend in labeling.

4. Has acceptable safety been demonstrated?

Turning to safety considerations, I believe it is fair to say that no safety findings have emerged from the patients in the 2 controlled trials and the German cohort that would preclude approval, though this experience did demonstrate Novantrone's effects on the heart (dose related decrease in Ejection Fraction in Study 0901), hematologic system (decreased WBC and neutrophil counts), GI system (nausea and vomiting), and possibly renal system (dose related increased incidence of UTI).

However, use of Novantrone can be associated with serious toxicity, especially to the heart and bone marrow, and this toxicity is believed to be primarily related to cumulative dose (although the post-marketing experience suggests that CHF can occur at relatively low doses, even possibly after a few doses). As Dr. Boehm notes, most articles in the literature have identified a cumulative risk of CHF of about 2% to 120 mg/m^2, after which the risk seems to rise steeply above about 160 mg/m^2.

MS is, of course, a chronic illness, and it is expected that any treatment approved for these patients could be given indefinitely. Indefinite use of Novantrone, however, poses the problem of potentially irreversible, life threatening toxicity; a limitation on the number of courses of treatment would be a highly unusual outcome for a treatment directed at a chronic illness. In addition, use of Novantrone in patients with MS could be restricted to physicians experienced in the use of chemotherapeutic agents, oncologists specifically, or other restrictions on its use could be considered (e.g., only administered in tertiary care centers, etc).

The Committee addressed this question as well, and felt that no specific restrictions should be placed on Novantrone's use in MS patients. The sponsor offered that they would limit the maximum cumulative dose to 140 mg/m^2 in any one patient.

COMMENTS

The PCNS Advisory Committee voted unanimously that the sponsor had submitted substantial evidence of effectiveness to support a claim similar to the one proposed, and also that sufficient evidence of safety had been submitted.

While I agree that the application can be considered Approvable, I do believe that additional data needs to be submitted before an Approval action can be taken.

Specifically, although the Committee was satisfied that patients in Study 902 were "progressive", or had "aggressive" disease, despite their having been diagnosed as relapsing-remitting patients, I believe that the sponsor should submit evidence that further establishes this point. In particular, I believe that the sponsor should submit evidence that these patients were not normal between relapses, and that their disease had, in fact, progressed over time. It will be particularly important for the sponsor to demonstrate, for example, that the EDSS scores obtained on these patients, and presumably accurately

representing the patients' inter-relapse state, were not obtained during, or close in time to, a relapse.

In addition, I believe the sponsor should document the progressive nature of the disease in patients enrolled in Study 901.

Further, because the EDSS was rated by an unblinded observer in Study 902, we have no valid independent replication of the finding on neurologic status (as measured by EDSS) ostensibly seen in Study 9001. For this reason, before a claim can be granted for an effect on neurologic status, we should be assured that the effect seen in Study 901 was a robust one. One way to determine this would be for the sponsor to document that any effect on EDSS, once seen persisted over time (e.g., 3-6 months). We will ask the sponsor for this documentation.

Finally, I believe it is critical for the sponsor to document that the relapses in both trials, were, in fact, serious by reasonable criteria. If the sponsor cannot document that this was so, I believe it would be inappropriate to grant a claim for an effect on relapse, regardless of the Committee's recommendations.

In addition to the clinical data that we will request, I believe that it is also critical that the sponsor submit in vitro metabolism data for Novantrone. The metabolism is poorly characterized at this time, but the introduction of this treatment into the MS population requires, in my view, some basic information about metabolism and potential interactions with other drugs this population may be exposed to. Also, as noted by Dr. Al-Habet, the sponsor has considerable additional metabolism/kinetic work to do, some of which has been discussed with them over several years, arising in the context of their prior submissions. We will ask that they commit to producing this data in Phase 4.

We have also discussed with the sponsor the establishment of a registry for patients with MS who will receive Novantrone. Because the risk of cardiac failure is real in this population, although we do not have a reliable estimate of the incidence in this population, it seems prudent to require all patients to register with a central monitor when treatment is initiated. In this way, patients could be followed over time, and when they approach a cumulative dose of 100 mg/m^2, cardiac monitoring could be assured. Further, such a registry would have the ability, at least in theory, to assure that a given patient does not ordinarily receive a cumulative dose of greater than 140 mg/m^2. The specifics of this registry will need to be discussed with the sponsor.

With regard to labeling, the attached draft label contains specific language we would like the sponsor to adopt, as well as notes to which they will need to respond. Of note, we believe that the label should be accompanied by patient labeling. The letter asks the sponsor to draft such patient labeling in the form of a Medication Guide, as described in 21 CFR 208.20. Whether this will ultimately take the form of a Medication Guide or a patient package insert will be determined.

ACTION

I will issue the attached Approvable letter with the included draft labeling.

/S/

Russell Katz, M.D.

Cc:
NDA 21-120
HFD-120
HFD-120/Katz/Rouzer-Kammeyer/Boehm/Wheelous
HFD-860/Al-Habet
HFD-710/Yan/Jin

APPEARS THIS WAY
ON ORIGINAL

Wheelous

MEMORANDUM OF TELEPHONE CONVERSATION
NDA 21-120

Drug: Novantrone i.v. For Multiple Sclerosis
Sponsor: Immunex
Date: February 24, 2000
Conversation Between:

Agency:
Dr. R. Katz – Division Director
Ms. T. Wheelous – Project Manager

Sponsor:
M. Gauthier – Sr. Reg. Affairs Mngr.
Dr. D. Viveash – Reg. Affairs
Ms. Nancy - Reg. Affairs

Purpose: Discussion regarding the status of forthcoming NDA action letter.

Discussion:

I Request for Action Letter without Draft Labeling

✦Dr. Katz stated that as a result of the Advisory Committee Meeting held January 28,2000,the Agency's request for more data will be included in the Action letter.

✦Immunex inquired about the possibility of the Division issuing an action letter without draft labeling. Dr. Katz said that the action letter will have draft labeling containing some changes to the Immunex proposed labeling as well as some "Note to Sponsor" sections requesting additional sections to labeling, such as tables.

✦There will be some room for label negotiation after receipt of the resubmission.

✦The action letter should issue sometime early next week.

II Requirement for PK Data Prior to Approval

✦Immunex was informed that in vitro metabolism data will be required prior to approval and this deficiency will be stated in the action letter. The specific studies may be discussed with the Biopharmaceutics Division after the issuance of the action letter.

✦Immunex was reminded that PK data was requested many times prior to the submission of this NDA.

III Patient Labeling (Draft)

✦ Given the cardiac toxicity concerns associated with Novantrone a patient package labeling is necessary. This patient labeling should contain information about the cardiac symptoms that patients should be aware of.

✦Also, patients should be instructed of the appropriate steps to be taken once the maximum cumulative dose is obtained.

ACTION ITEMS:
The Division will issue an action letter early next week.

cc: Orig NDA 21-120
HFD-120
/Katz
/Wheelous
/Rouzer
/Boehm
Draft: March 28, 2000
C:\wheelous\nda\novantrone\22400telecon.doc
TELECON

/S/ 3/27/00
3/28/00

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 18 2000

Mark A. Gauthier
Senior Manager, Regulatory Affairs
Immunex Corporation
51 University Street
Seattle, WA 98101-2936

RE: Refund of Application Fee for Novantrone, NDA 21-120

Dear Mr. Gauthier:

This letter responds to your letter dated August 30, 1999, requesting a refund of the application fee paid under the Prescription Drug User Fee Act of 1992 (PDUFA) as amended by the Food and Drug Administration Modernization Act of 1997 (Modernization Act) for review of your new drug application (NDA) for Novantrone (mitoxantrone for injection) (NDA 21-120).

Your request for a refund is based on the exception for products designated as orphan drugs (section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (the Act)). You state that Immunex Corporation (Immunex) submitted NDA 21-120 on June 2, 1999, accompanied with an application user fee payment of $272,282. According to your letter, on August 13, 1999, the Office of Orphan Products Development informed Immunex that Novantrone had received orphan drug designation for the secondary-progressive multiple sclerosis and progressive-relapsing multiple sclerosis indications. For the reasons described below, the Food and Drug Administration (FDA) grants your request for a refund of the application fee paid for Novantrone NDA 21-120.

Our records show that in 1984, Novantrone was submitted to FDA's Division of Oncology Drug Products under NDA 19-297 for the following two indications: (1) for initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer, and (2) in combination with other approved drugs, for the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults, which includes myelogenous, promylocytic, monocytic, and erythroid acute leukemias. In June 1999, Novantrone NDA 21-120 was submitted to FDA's Division of Neuropharmacological Drug Products for approval of the following two new indications: (1) for the treatment of patients with secondary-progressive multiple sclerosis, and (2) for the treatment of progressive-relapsing multiple sclerosis. Novantrone NDA 21-120 was submitted as a

Type 6 application, and for user fee purposes, Type 6 applications are treated as efficacy supplements.[1]

Under the PDUFA as amended by the Modernization Act, a supplement proposing to include a new indication for a rare disease or condition in a human drug application is not subject to an application fee if the drug has been designated under section 526 as a drug for a rare disease or condition with regard to the indication proposed in the supplement (section 736(a)(1)(E) of the Act).

Our records also show that we received Novantrone NDA 21-120 on June 4, 1999, and we received a payment of $272,282 on June 8, 1999. We have verified that on August 13, 1999, Immunex received orphan drug designation for Novantrone's indications for the treatment of secondary-progressive multiple sclerosis and for the treatment of progressive-relapsing multiple sclerosis. Because this Type 6 application is treated as a supplement and the Type 6 application proposes indications that are orphan designated, an application fee for Novantrone NDA 21-120 is not required. Your request for a refund is granted. Please note that the Act does not exempt orphan drug products from the annual product and establishment fees.

We have asked the Office of Financial Management to issue a refund of the $272,282 payment you submitted for the review of this NDA. If you do not receive a check by March 10, 2000, please call Mr. Michael Roosevelt, Chief, Systems Accounting Branch, at 301-443-4872.

If you have further questions concerning user fees, please contact Michael Jones or Beverly Friedman at 301-594-2041.

Sincerely,

/S/

APPEARS THIS WAY
ON ORIGINAL

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

[1] FDA, *Attachment D - Application, Product, and Establishment Fees: Common Issues and Their Resolution*, December 16, 1994, which can be found on the Internet at www.fda.gov/cder/pdufa/default.htm.

Wheelous

MEMORANDUM OF TELEPHONE CONVERSATION
NDA 21-120

Drug: Novantrone i.v. For Multiple Sclerosis
Sponsor: Immunex
Date: February 10, 2000
Conversation Between:

Agency:	Sponsor:
Dr. R. Katz – Division Director	M. Gauthier – Sr. Reg. Affairs Mngr.
Dr. J. Rouzer – Kammeyer – Medical Reviewer	Dr. R. Stead – V.P., Clinical Dev.
Dr. G. Boehm – Safety Reviewer	Dr. A. Hayes – Sr. V.P., Clin Dev.
Ms. T. Wheelous – Project Manager	Dr. A. Rubin - Biometrics
	Dr. D. Viveash – Reg. Affairs
	Dr. R. Ghali – Director, Ciin Dev.
	Dr. M. Butine - Biometrics

Purpose: Discussion regarding the forthcoming NDA action and information request resulting from the January 28, 2000 Advisory Committee Meeting.

Discussion:

I PCNS Advisory Committee Meeting (ACM)

Dr. Katz recalls that the committee made its recommendations based upon data that the Agency was not aware of. At the ACM, the sponsor clarified that the patients had "progressive" disease because their inter-relapse neurological condition was not normal, and that the patients worsened over time prior to enrollment. The sponsor must submit documentation to support this. In addition, the sponsor should submit documentation that the EDSS scores were not assessed during relapses.

The unblinding of the relapse data continues to be a concern. In an attempt to validate the unblinded relapse data please provide the relapse distribution rates based upon the two definitions of serious relapses. The two definitions of serious relapses provided are (1) an increase on the EDSS by 2 points during a relapse, and (2) an increase on the functional measures by one point.

Immunex replied to an inquiry that 36-month MRI data for study #01 is not available.

II Proposed Labeling

➡The Division has not yet reviewed the proposed labeling in detail. However, when the time comes for detailed labeling the Oncology Division, the Division that will be responsible for the product after the approval action of this type 6 NDA, will be consulted.

➡The current Box Warning in labeling does not address the cumulative dosing concern as it relates to this new patient population, i.e., Multiple Sclerosis population, and their (non-oncology) prescribers.

➡Immunex should draft some language for the Box Warning section that will address the cumulative dose issue and maybe insert a directive to see WARNINGS section of labeling.

III Two Orphan Drug Designations and Possible Concern about Change in Qualification.

➡ Currently Novantrone has been granted two different Orphan designations, worsening relapsing-remitting MS and secondary progressive MS. These are the two categories of MS proposed for indication in labeling.

➡Immunex has a concern that if the product is approved for both categories, the combined disease population will be greater than the [redacted] restriction imposed by Orphan disease definition.

IV Registry Proposal

➡The February 07, 2000 fax provides for a document titled, "Proposed Registry to Evaluate the Safety of Novantrone in the Management of Multiple Sclerosis". Immunex proposes [redacted]

➡The sponsor will consider the Division's preferences and propose an alternative registry.

➡At the PCNS ACM, Dr. Temple discussed the possibility of not limiting the cumulative dosing to 140 mg/m^2 as the product is currently labeled, but rather allow higher doses to be administered in the MS patients while obtaining additional safety data. [redacted]

ACTION ITEMS:

1 Immunex will submit a revised registry plan.
2 Immunex will submit revised labeling with added language to the Box Warning section.
3 Dr. Katz will discuss alternate dosing regimen study with Dr. Temple

cc: Orig NDA 21-120
HFD-120
/Katz /S/
/Wheelous
/Rouzer /S/
/Boehm
Draft: February 16, 2000
Final:
C:\wheelous\nda\novantrone\210200telecon.doc
TELECON

APPEARS THIS WAY
ON ORIGINAL

immunex

Immunex Corporation
Regulatory Affairs
51 University Street
Seattle, WA 98101

Phone: 206 389-4066
Fax: 206 223-0468

FAX MESSAGE - PLEASE DELIVER IMMEDIATELY

Send to: Teresa Wheelous ~~Jack Purvis~~ Fax: (301) 594-2858

From: Mark W. Gauthier Date: February 8, 2000

Total Number of Pages: 2 INCLUDING THIS PAGE

COMMENTS: **Re: NDA 21-120, Novantrone (mitoxantrone hydrochloride)**

Dear Ms. Wheelous:

Please consider this a formal request for a teleconference with Dr. Al-Habet, the Clinical Pharmacologist who took part in our meeting on January 19, 2000. Immunex participants would include Dr. Mark Rogge, Director of Pharmacology and Toxicology, and me. We would like to schedule the telecon with Dr. Al-Habet as soon as possible to determine precisely what is needed to address the issues he raised at the 1/19 meeting. The issues include:

- Review of published pharmacokinetic data on Novantrone (see attached table - not included in NDA 21-120)
- Proposal for studying potential drug interactions

Our proposal would be to do additional studies, if any are considered necessary, post-approval.

Please forward this request to Dr. Al-Habet and ask him to call me at (206) 381-6266 to arrange the teleconference.

Thank you.

APPEARS THIS WAY ON ORIGINAL

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Manager, Regulatory Affairs

File 31100

immunex

Immunex Corporation
Regulatory Affairs
51 University Street
Seattle, WA 98101

Phone: 206 389-4066
Fax: 206 223-0468

FAX MESSAGE - PLEASE DELIVER IMMEDIATELY

Send to: Jack Purvis Fax: (301) 594-2858

From: Mark W. Gauthier Date: February 7, 2000

Total Number of Pages: 3 INCLUDING THIS PAGE

COMMENTS: **Re: NDA 21-120, Novantrone (mitoxantrone hydrochloride)**

Dear Mr. Purvis:

As we discussed by phone earlier, attached please find a copy of Immunex Corporation's proposal for a patient registry that we would commit to do post-approval for Novantrone for the treatment of MS. Please distribute copies of this document to the members of the review team prior to the internal meeting scheduled for Tuesday 2/8. We plan to discuss this during the teleconference scheduled for Thursday 2/10 at 3:30 pm ET.

Thank you for your assistance and please call me at (206) 381-6266 if you have any questions.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Manager, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

Number of Pages Redacted 2

Number of Pages Redacted 19 pages

❖❖❖

Confidential,
Commercial Information

(6)