CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-855

Administrative Documents

ASTA MEDICA

NEW DRUG APPLICATION
FD FORM 356H
SECTION d(1);

MESNA TABLETS

Application Summary

Title: **Patent Certification**

ASTA MEDICA

NEW DRUG APPLICATION
FD FORM 356H

MESNA TABLETS

Patent Certification

Patent Number: 5,252,341

Expiry Date: 8/17/2012

Type of Patent: Tablets and granulates containing mesna as active substance

Name of Patent Owner: Asta Medica Akiegesellschaft, Fed. Rep. Of Germany

Name and Address of Agent: Aileen Ryan, Asta Medica, Inc. Hackensack, NJ

Original Declaration:

The undersigned declares that Patent No. 5,252,341covers the formulation, composition and/or method of use of Mesnex (mesna) Tablets. This product is the subject of this application for which approval is being sought.

Aileen Ryan
Vice President Regulatory Affairs and Compliance
ASTA Medica, Inc.
Hackensack, NJ

Patent Number: 5,262,169

Expiry Date: 07/16/2011

Type of Patent: Tablets and granulates containing mesna as active substance

Name of Patent Owner: Asta Medica Akiegesellschaft, Fed. Rep. Of Germany

Name and Address of Agent: Aileen Ryan, Asta Medica, Inc. Hackensack, NJ

Original Declaration:

The undersigned declares that Patent No. 5,262,169covers the formulation, composition and/or method of use of Mesnex (mesna) Tablets. This product is the subject of this application for which approval is being sought.

Aileen Ryan
Vice President Regulatory Affairs and Compliance
ASTA Medica, Inc.
Hackensack, NJ

EXCLUSIVITY SUMMARY for NDA # 20-855 SUPPL # 000
Trade Name Mesnex Tablets Generic Name mesna tablets
Applicant Name Bristol Myers-Squibb /Baxter Oncology HFD-150
Approval Date 3-21-02

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO / /

   b) Is it an effectiveness supplement? YES / / NO / X /

   If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES / X / NO / /

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

   d) Did the applicant request exclusivity?

   YES / / NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X_/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #	19-884	mesna inject
NDA #		
NDA #		

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # D-07093-3126

Investigation #2, Study # D-07093-0018

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 3126 YES /___/ NO /_X_/

Investigation #2 0018 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 3126 YES /___/ NO /_X__/

Investigation #2 0018 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # 3126

Investigation #__, Study # 0018

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # [redacted] YES /___/	NO /_X__/ Explain: _Asta__ Medica was the sponsor (They were bought by Baxter Oncology)
Investigation #2	
IND # [redacted] YES /___/	NO /X___/ Explain: Bristol-Myers Squibb transferred study 3126 & cross referenced to Asta Medica IND 2/12/01

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title

/S/

_____ 3/21/02

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

ASTA MEDICA

NEW DRUG APPLICATION
FD FORM 356H
SECTION d(1);

MESNA TABLETS

Application Summary

Title: **Claimed Exclusivity**

In accordance with 314.108(b)(4) ASTA Medica, Inc. is claiming an exclusivity period of three years for mesna tablets. Mesna in an injection solution under the tradename Mesnex® Injection, was approved for the prevention of ifosfamide-induced hemorrhagic cystitis in December 1988 under NDA#19,884.

This NDA is for an oral formulation, Mesnex® (mesna) Tablets will be used in an intravenous plus oral dosing regimen for the prevention of ifosfamide induced hemorrhagic cystitis.

The drug product, mesna tablets, containing all of the same active ingredients with the same conditions of approval, has not been previously approved.

In 1991, ASTA Medica filed an IND for mesna tablets. The clinical study D-07093-0018 (MR9205002a) conducted under this IND, is the primary adequate and well-controlled study in this NDA supporting the efficacy of the intravenous plus oral dosing regimen of mesna using the tablets. This study was designed in accordance with the recommendations from the Division of Oncologic DrugProducts at FDA. At the pre-NDA meeting held in August 1996, the Division of Oncologic Drug Products agreed to accept an NDA with an interim analysis of this study as the primary efficacy data. The other clinical studies included in this NDA were sponsored, conducted and funded by our parent company ASTA Medica AG. A list of the clinical investigations other than bioavailability or bioequivalence studies, conducted by ASTA Medica, Inc. and its parent company, ASTA Medica AG, is provided together with the location of the study in the Clinical Data Section of the NDA.

To the best of our knowledge, these published studies have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved New Drug Application or supplement.

We believe that the above referenced studies are essential to the approval of this NDA for Mesnex® (mesna) tablets. Attached is a summary of the information available in the literature on orally administered mesna. There are no published studies which meet FDA's definition of adequate and well-controlled studies which could be used to document the efficacy and safety of Mesnex (mesna) Tablets.

MESNA TABLETS

Application Summary

Based on these data, we conclude that the studies included in this submission were essential for the approval of mesna tablets. As a result, we are requesting 3 years of exclusivity upon approval of this NDA.

Aileen Ryan
Vice President
Regulatory Affairs and Compliance
ASTA Medica, Inc.

MESNA TABLETS

Application Summary

Study	Vol in Clinical Data Section
D-07093-0018; MR9205002a; Medic #501, Comparative, 2-way crossover multiple dose study of efficacy and safety of an iv and an iv/oral regimen of mesna in patients treated with Ifosfamide	41-45
MED504 European multicenter randomized parallel group study (phase II) of the efficacy and safety of two regimens of Mesna in patients treated with Ifosfamide	47-50
D-07093-0019; MRS 9104001 Multiple dose urinary and serum pharmacokinetics of Sodium-2-Mercaptoethanesulfonate (mesna and dimesna) after oral and intravenous administration to patients treated with Ifosfamide (DP 172)	34-36
Internal Report D-07093-2200000010 on Study No D-07093-0016, Amendment No. 1 to the report: Clinical Phase II trial to evaluate the uroprotective effect of mesna film-coated tablets (600 mg) in intravenous Ifosfamide schedules. May 3, 1995	54-55
Interim Study Report Open, Multiple Dose Study of the Efficacy and Safety of a Regimen of Mesna Tablets in Patients Treated with Ifosfamide (MEO Study #700)	51-52
Becker, Study D-07093-0011, Clinical Phase II crossover trial of mesna given intravenously and as film-coated tablets in patients with metastasized breast cancer treated according to protocol - a pilot study	53
Cerny, T., Study MED200, D-07093-0012 Combined oral & intravenous uroprotection with Mesna in Ifosfamide treated patients	53

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

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.

NDA/BLA # 20-~~890~~ 855 Supplement # 000 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 ____ Trade and generic names/dosage form: Mesnex Tablets Action: AP AE NA

Applicant BMS/ Baxter Oncology Therapeutic Class _____

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate X inadequate __
Proposed indication in this application Prevention of ifsofamide induced hemorrhagic cystitis

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) _X__No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 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.

X 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.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes _X__No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

's page was completed based on information from Pediatric waiver request 7/19/01 & Granted letter 8/14/01
g., medical review, medical officer, team leader)

/S/

Signature of Preparer and Title Debra Vause, project manager Date 3/15/02

cc: Orig NDA/BLA # 20-855
HFD-150 /Div File
NDA/BLA Action Package
HFD-960/ Peds Team
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

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.

~~BLA~~ # NDA 20-855 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 Trade and generic names/dosage form: MESNEX (mesna) TABLETS Action: AP AE (NA)

Applicant Asta Medica Therapeutic Class _____

Indication(s) previously approved Detoxicant (Ifosfamide-Induced Hemorrhagic Cystitis Prophylaxis)
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___
Proposed indication in this application Prevention of Ifosfamide-Induced Hemorrhagic Cystitis

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 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.

X 5. If none of the above apply, attach an explanation, as necessary.
This application was not approved

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ___No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

S

Signature of Preparer and Title

3/20/98
Date

Orig NDA/~~BLA~~ # 20-855
HFD-150 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

ASTA MEDICA

Mesna Tablets

NDA, FD Form 356H, Section d (1)

This is to certify that ASTA Medica did not and will not use any capacity the services of any person debarred under section (a) or (b) (section 306 a or b), in connection with this NDA application for Mesnex (mesna) Tablets.

ASTA Medica AG
Registration Department

i.V.

Dr. Wolfgang Fischer

i.V.

Dr. Rose Quadbeck Diel

Frankfurt, 31.05.01

ASTA MEDICA

NEW DRUG APPLICATION
FD FORM 356H
SECTION d(1);

MESNA TABLETS

Application Summary

Title: **Debarment Certification**

This is to certify that ASTA Medica did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) {section 306(a) or (b)}, in connection with this NDA application for Mesnex (mesna) Tablets.

Aileen Ryan
Vice President
Regulatory Affairs and Compliance
ASTA Medica, Inc.

(792)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee

Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Oncology Drug Products	**HFD-150**
Attention: Josephine Jee, Chemist Leslie Vaccari, Project Manager	**Phone:** 594-1512 594-5778
Date: April 2, 1997	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Mesnex Tablets 400 mg	**NDA** 20-855
Established name, including dosage form: mesna tablets	
Other trademarks by the same firm for companion products: Mesnex (mesna) for Injection	
Indications for Use (may be a summary if proposed statement is lengthy): Mesnex has been shown to be effective as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic	
Initial Comments from the submitter (concerns, observations, etc.):	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month.
Please submit this form at least one week ahead of the meeting.
Responses will be as timely as possible.

Original NDA 20-855
HFD-150/Division file
HFD-150/L.Vaccari
HFD-150/JJee

Consult #792 (HFD-150)

MESNEX mesna tablets 400 mg

MESNEX is an already approved parenteral product used as a detoxifying agent. The sponsor is seeking a new indication with a tablet formulation for ifosfamide induced hemorhage. The Committee has no concerns about the use of the name MESNEX for the new dosage form and indication.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 6/23/97, Chair
CDER Labeling and Nomenclature Committee

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

RHW 4-2-97

TO (Division/Office):	FROM: Division of Oncology Drug Products HFD-150
Dan Boring, Chemist HFD-530/CRP2 N461	Leslie Vaccari,PM/Josephine Jee,Chemist

E	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2 April 1997		20-855	Pending NDA	20 March 1997

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
MESNEX (mesna)Tablets		3	4 Months

NAME OF FIRM: Asta Medica

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:
  Trademark Review new NDA

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

See Attachment

45 Day Meeting - 12 May 1997

If I can be of any assistance please call me at 594-5778 or EMail me.

cc: Original NDA 20-855
HFD-150 Div File
HFD-150/JJee
HFD-150/LVaccari
HFD-150/RWood

SIGNATURE OF REQUEST	METHOD OF DELIVERY (Check one)
/S/ 4-2-97	☐ MAIL ☑ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Vause, Debra

From: Carter, Linda S
Sent: Friday, September 14, 2001 11:44 AM
CDER-ORM-PM
ct: Action packages

Financial disclosure submissions from the applicant no longer need to be included in the action package. Currently, the actual financial disclosure submission provided by the applicant is sometimes included in the action package. This has been helpful in the past during the early implementation of the financial disclosure regulation. However, the review staff understands the financial disclosure regulations now, and medical officers are to address financial disclosure in their reviews. Therefore, generally there is no need to provide the actual submission. If there is a question about financial disclosure, the ADRA can request the submission from the division. Not including the submission in the action package will save FOI the work of having to redact it, and will prevent inadvertent release of the submission to the public. Thanks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996.

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

ASTA Medica, Inc.
401 Hackensack Avenue
Hackensack, NJ 07601

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

ASTA Medica, Inc.
401 Hackensack Avenue
Hackensack, NJ 07601
Aileen Ryan

3. TELEPHONE NUMBER *(Include Area Code)*
201-525-2680

4. PRODUCT NAME
Mesna Tablets

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☒ YES ☐ NO
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
3223

7. LICENSE NUMBER/NDA NUMBER.
20,855

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES *(See reverse if answered YES)* ☒ NO

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES *(See reverse if answered YES)* ☒ NO

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Vice President, Regulatory Affairs & Compliance	March 20, 1997

FDA 3397 (12/93)

Printed by Leslie Vaccari

Electronic Mail Message

tivity: COMPANY CONFIDENTIAL

Date: 13-Oct-1997 03:09pm
From: Gerald Sokol
SOKOL
Dept: HFD-150 WOC2 2103
Tel No: 301-594-2473 FAX 301-594-0498

TO: See Below
Subject: RE: Mesna Request for Information

Yes-I would wish them to explain if possible the grossly uneven number of deaths that occurred in the iv/po/po arm.

Jerry

Distribution:

TO: Julie Beitz	(BEITZJ)
CC: Z. John Duan	(DUANJ)
CC: Gang Chen	(CHENGA)
CC: Atiqur Rahman	(RAHMANA)
CC: Leslie Vaccari	(VACCARIL)
CC: Gurston Turner	(TURNERG)
CC: Robert DeLap	(DELAPR)

Printed by Leslie Vaccari

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 10-Oct-1997 12:45pm
From: Leslie Vaccari
VACCARIL
Dept: HFD-150 WOC2 2092
Tel No: 301-594-578 FAX 301-827-4590

TO: Gurston Turner (TURNERG)

CC: Julie Beitz (BEITZJ)
Subject: Status of inspection reports

Hi,

NDA 20-855 Mesnex Asta Medica

Just wanted to follow-up after our meeting last week regarding the status of the final reports for

Also, what will be the timing of your applicant inspection on Asta?

Thanks for the info.

Leslie

Printed by Leslie Vaccari

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 31-Jan-1997 03:14pm
From: Atiqur Rahman
RAHMANA
Dept: HFD-860 WOC2 2041
Tel No: 301-827-1529 FAX 301-594-0498

TO: Leslie Vaccari (VACCARIL)

CC: Elena Mishina (MISHINAE)
Subject: Re: Mesna IND

Leslie:
Yes, they can. Four weeks will be well within 45 d filing meeting date.
Atik

Hi,

For my clarification, they can submit the data on 2 lots (12 tablets, 3 media) in the NDA and follow with the 3rd lot four weeks after NDA submission.

Thanks Leslie

Printed by Leslie Vaccari

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 01-Apr-1997 05:20pm
From: Atiqur Rahman
RAHMANA
Dept: HFD-860 WOC2 2041
Tel No: 301-827-1529 FAX 301-594-0498

TO: Leslie Vaccari (VACCARIL)

Subject: Mesna NDA

Hi Leslie:

John Duan will be the assigned Clin Pharm Biopharm reviewer for Mesna. Please include John in the team and take off Elena as a reviewer.
Thanks.
Atik

Vaccari

MEMORANDUM of MEETING

DATE: May 12, 1997 11 am Conference Room B

NDA 20-855 Mesnex (mesna) Tablets APPLICANT: Asta Medica

MEETING PURPOSE: 45 Day Meeting - Internal

ATTENDEES:

Medical :	Gerald Sokol, M.D./ Julie Beitz, M.D.
Statistics:	Gang Chen, Ph.D.
Pharmacology:	Wendy Schmidt, Ph.D./Paul Andrews, Ph.D.
Biopharmaceutics:	John Duan, Ph.D./Atiqur Rahman, Ph.D.
Chemistry:	Josephine Jee
Project Manager:	Leslie Vaccari

DISCUSSION TOPICS:

1. Status reports - IS APPLICATION ACCEPTABLE FOR FILING?
   Yes, file Clinical - ODAC presentation is not anticipated at this time
   Yes, file Chemistry
   Yes, file Pharmacology/Toxicology
   Yes, file Clinical Pharmacology and Pharmacokinetics (Sponsor responding to requests prior to filing date.)
   Yes, file Statistics

   All reviewers agreed that there were no filing issues and that the application was sufficiently complete to file. The application is a 3S.

3. All agreed to the following reviewing timeline:
   - The target date for first completed reviews is mid-November 1997 (9 months).
   - The preference for timing of team meetings is August/Sept/Nov/Dec/Jan(if needed)
   - Team GOAL for action - Dec 1997
   - Scheduled Team Meetings
     5 month mtg - August 5, 11-12 B
     6 month mtg(late) - September 29, 1-2 B
     8 month mtg (early)- November 3, 1-2 B
     9 month mtg - December 1, 1-3 B
   - Action Package to leave Division - not decided at this time

Conclusion: NDA 20-855 will be considered filed on May 24, 1997.

/S/ 6-12-97
Minutes Preparer, Project Manager

cc: Original NDA 20-855
HFD-150/Div file
HFD-150/All attendees

MEMO of MEETING - 45 Day Filing Meeting

MEMORANDUM OF MEETING

NDA 20-855 Mesnex (mesna) Tablets

DATE: 21 April 11-12 Conf Room B

MEETING PURPOSE: 21 Day Team Meeting

ATTENDEES: Primary Reviewer/ Team Leader

Medical :	Gerald Sokol ,M.D./ Julie Beitz, M.D.
Statistics:	Gang Chen, Ph.D./ Clare Gnecco, Ph.D.
Pharmacology:	Wendy Schmidt, Ph.D.
Biopharmaceutics:	John Duan, Ph.D.
Chemistry:	Rebecca Wood, Ph.D., Team Leader
Project Manager:	Leslie Vaccari

DISCUSSION ITEMS with DECISIONS REACHED:

- **Medical** - Has not completed filing review but application appears adequate at this point. There are no requests for the firm at this time. Dr. Beitz stated that following discussion with both Dr. Justice and Dr. DeLap that this application has been determined to be standard.
- **Statistical** - Dr. Chen has the following requests to be conveyed to Asta: 1. Please provide a detailed directory of SAS programs for efficacy analysis (i.e., programs written for what analyses) and 2. Locations of data for SAS programs are not clear, for example the location of the data in SAS program TAB34.sas is BIOMDSK: [000000.d07093.st0018]. This name was not found in the diskettes. Please clarify those names of data given in the diskettes to match those used in the SAS programs.
- **Pharmacology/Toxicology** - Review is complete and with Dr. Andrews for sign-off.
- **Biopharmaceutics** - Requests for additional information will be available in the next two days to be conveyed to the sponsor. The plasma pharmacokinetic study report should be submitted before the filing date for our review. This was agreed to at the pre-NDA meeting.
- **Chemistry** - Dr. Wood reported that there are no problems at this time.
  - Stability Statistical Consult - no report
  - CDER Labeling and Nomenclature Committee - Sent
  - EA - will be done by Josephine Jee
  - Establishment Inspection - no report
- **Microbiology - Tablets-** not needed for tablet
- **Project Management** - All agreed that the exact timeline and target dates for this standard review application will be decided at the 45 Day Filing Meeting. Everyone should come to the 45 Day Filing Meeting ready to discuss and decide on an appropriate review timeline.

b (5)

ACTION ITEMS:

1. b(5)

Dates to know for planning:

3 mth mtg - June 23
4 mth mtg - July 21
5 mth mtg - Aug 25
6 mth mtg - Sep 22
7 mth mtg - Oct 20
8 mth mtg - Nov 24
9 mth mtg - Dec 22
10 mth mtg - Jan 21
11 mth mtg - Feb 18

2. Leslie will fax stat and Pk requests to the sponsor.

cc:
Original NDA
HFD-150/DIV FILE

MEMORANDUM OF MEETING - 21 Day Meeting

MEMORANDUM OF TELECON

DATE: January 27, 1997 **TIME:** 3:00 pm **Location:** "B" WOC-2

IND/DRUG: [redacted] Mesna tablets **SPONSOR:** Asta

PURPOSE OF TELECON: Meeting requested by Asta to discuss further the data required for the determination of a waiver of required bioequivalence study.

PARTICIPANTS:

FDA (HFD-150)
Atiqur Rahman
Elena Mishina
Leslie Vaccari

ASTA
Aileen Ryan, Vice President, Regulatory Affairs and Compliance

DISCUSSION POINTS and DECISIONS (agreements) REACHED:

1. Ms. Ryan clarified that for the clinical supplies used in the studies, [redacted] at Asta's production facility, [redacted]
For the to-be-marketed product in the NDA submission, all [redacted] will be consolidated at the [redacted]
a subsidiary of Asta Medical AG. The formulation of the tablets remains the same for clinical supply and to-be-marketed,.

2. In addition to the previously requested data, complete information on the [redacted] be-marketed formulation is needed. Tablet profile must be provided on 12 tablets in three lots from [redacted] and 12 tablets in two lots from [redacted] It will be acceptable to submit the data on the third lot from [redacted] four weeks after NDA is submitted. Dissolution data using the basket method is preferred in three media, but we will accept two media with time points at [redacted] minutes. Ms. Ryan agreed.

The telecon concluded at 3:10 pm.

/S/ 2-20-97 Concurrence: /S/ 2/22/97
Project Manager
Minutes preparer

cc:
Original IND [redacted]
HFD-150/Div File
/EMishina
/LVaccari

Drafted by: LVaccari/2-20-97

MEMORANDUM OF TELECON

MEMORANDUM OF MEETING

DATE: September 10, 1996 2:00-3:00 pm Conf A WOC II

IND/DRUG [redacted] Mesnex (mesna) Tablets 400mg

SPONSOR: Asta Medica

MEETING PURPOSE: CMC Pre-NDA Meeting
(Briefing Document submitted June 14, 1996)

ATTENDEES:

FDA

Rebecca Wood, Ph.D. Supervisory Chemist
Josephine Jee, Reviewing Chemist
Leslie Vaccari, Project Manager

SPONSOR

Eileen Ryan, Regulatory Affairs
Dr. Elisabeth Wolf-Heuss, Director,Head of Pharm. Development, Asta Medica Aktiengesellschhaft
Dr. Bernd Dolle, Head of Pharm.Manufacturing, Asta Medica Aktiengesellschhaft
Dr. Fischer, Asta Medica Aktiengesellschhaft

SUMMARY:

1. Question: *Item #3 in question list in briefing document submitted June 14, 1996. The manufacturing site for [redacted] the tablets has been moved from our [redacted] facility to [redacted] plant. The process and equipment remain the same. We would like to confirm with the Division that comparative dissolution profiles and stability data are sufficient to document the comparability of the tablets manufactured at the two sites and that it is not necessary to conduct a bioequivalence study.*

   The sponsor stated that all manufacturing will now be done at the [redacted] facility in [redacted] The process and equipment will remain the same. Stability studies have been initiated on three lots which were manufactured August 29, 1996 at [redacted] The sponsor had release and dissolution profiles for presentation today but did not included the data in this briefing document. Because the information had not been provided for our review, the sponsor was requested to prepare a complete review document for the biopharmaceutics reviewer regarding the necessity for a bioequivalence study and submit it as soon as possible. The biopharmaceutics reviewer was not in attendance at today's meeting because no information or data had been provided in the briefing document. Dr. Wood added that bioequivalence is a concern and all data establishing bioequivalence between all clinical and manufactured batches must be provided.

2. Question: *Item #4 in question list. In support of the change in site of [redacted] the tablets, we have initiated studies on three lots. We would like to confirm that the Division will accept the NDA for filing with 3 months of accelerated and room temperature stability data.*

   Dr. Wood stated this was acceptable. 6 month stability data will be submitted within three months after the application is submitted.

3. Question: *Item #5 in question list. We are planning to consolidate all — in the production and packaging of mesna tablets at — facility. Since it is anticipated that this will be our primary manufacturing site, we would like to discuss with the Division the most practical way to incorporate this additional manufacturing site into our NDA submission.*

   Complete information on the drug substance and drug product should be submitted in the application. All documents must be provided in English. The facility must be ready for inspection when the NDA is submitted. In the briefing document, the batch records are in German. Please provide English translations for all documents. In addition, provide master production records.

4. Quesion: *Item #9 in question list. We have included in this package a proposal for an Abbreviated Evironmental Assessment. In addition we are aware of the draft proposal that would eleiminate the requiremnt for the EA for NDAs for products such as mesna tablets. We would like to obtain feedback from the Division as to whether the abbreviated document is sufficient or if the requiremnt can be waived on the basis of the draft regulation.*

   Dr. Wood suggested the sponsor contact Nancy Sager, HFD-357, regarding a specific response to this question. In general, the approach appears satisfactory.

5. Dr. Wood requested that the sponsor provide a table clearly defining the manufactured batch, the certificate of analysis and clinical study (note if pivotal). In addition, lot profile should be provided in a chart detailing everything for that specific lot.

6. Components and labeling of the blister pack was discussed. Specific identification of which — comes in direct contact with the tablet in the blister pack must be provided. — is not acceptable. The printed label on the — of the blister pack must include drug name, dose, manufacturer, expiration date and lot number.

ACTION ITEMS:

1. Asta will submit complete information on the comparative dissolution profiles to the IND for biopharmaceutics review as soon as possible.

2. Asta plans on submitting their NDA in January 1997.

/S/ 10-2-96

Project Manager
Minutes Preparer

cc: Original IND —
HFD-150/Div File
/LVaccari
/JJee
DPease

Drafted by: LVaccari/9-26-96/FT10-2-96
R/D init. by: RWood/9-30-96
JJee/9-30-96

MEMORANDUM OF MEETING - CMC PreNDA

MEMORANDUM OF MEETING

DATE: August 27, 1996 **TIME:** 2-3:30 pm **Conf Room** G-WOC2

IND/DRUG [redacted] Mesnex (mesna) Tablets

SPONSOR: Asta Medica, Inc.

MEETING PURPOSE: PreNDA Meeting (not including CMC) Indication: Alternate dosage form of Mesnex for the treatment of [redacted]

ATTENDEES:

FDA/HFD-150
Robert Temple, M.D., Office Director
Robert DeLap, M.D., Division Director
Robert Justice, M.D., Deputy Director
Gerald Sokol, M.D., Medical Officer
Clare Gnecco, Ph.D., Team Leader, Biostatistics
Gang Chen, Ph.D., Statistician
Wendy Schmidt, Ph.D., Pharmacologist
Elena Mishina, Ph.D., Biopharmaceutics
Atiqur Rahman, Ph.D., Team Leader, Biopharmaceutics
Derick Raghaven, M.D., ODAC Consultant by phone
Leslie Vaccari, Project Manager

Asta Medica

Wolfgang Brade, M.D., Medical Oncology
Marshall Goren, M.D., Clinical Pathologist
Klaus Junge, Ph.D., Biometrics Department

Aileen Ryan, Regulatry Affairs and Compliance
Ralph Venhaus, M.D., Medical Affairs
Klaus Gehringer, Ph.D., President of Asta Medica, Inc.

INTRODUCTION/PRESENTATIONS: Refer to attached agenda. CMC preNDA Meeting is scheduled for September 10, 1996.

DECISIONS REACHED:

1. Question: *Item #1 in question list in briefing document. Because of the slow recruitment in the ongoing US study, we would like to use the European clinical study included in Attachment 1 as the primary evidence of efficacy of mesna tablets. The safety, tolerance and pharmacokinetics studies conducted in volunteers and patients as well as the open efficacy studies conducted in Europe provide additional supportive safety and efficacy information. Assuming that a complete and valid report is included in the NDA and the data can be validated by on-site inspections, we would like to discuss the acceptability of*

this strategy with the Division. Our current plan is to continue the US study to completion, possibly with the addition of centers from Europe.

From a clinical perspective, the Agency believes that orally administered mesna tablets are likely to be effective; however, there are significant concerns with respect to the conduct of Study MEO-504. Specifically, this study is flawed in design and is easily subject to bias as a result of randomization utilizing the four-box technique. The numerous protocol deviations present serious problems. The patients who were determined to be unevaluable due to vomiting should actually be categorized as failures. The Fuchs Rosenthal-Chamber (FRC) data is not acceptable. The approach for the analysis of missing data is not appropriate. Therefore, when this application is submitted it should also include all available data from the ongoing US trial in addition to MEO-504.

2. Question: *We would like to confirm that this study in patients in connection with the previously reported bioavailability/pharmacokinetics studies in volunteers and the pharmacokinetics study in patients listed in Attachment 3, fulfill the requirements of the Division of Biopharmaceutics.*

   A study should be conducted in a minimum of eight patients or healthy volunteers to evaluate urine AUC as well as plasma concentration on days 1, 2 and 5. The study should be designed to provide data that will be adequate basis for labeling. Food study data will have to be provided to allow for appropriate labeling.

3. Question: *We would like to confirm that it is acceptable to incorporate this section of NDA 19-884 into the NDA for mesna tablets by reference.*

   Asta may reference all pharmacology/toxicology data in NDA 19-884 for the Mesnex Tablet proposed NDA. Asta should submit information detailing the formulations used in all preclinical studies to insure that all identified impurities are consistent between all formulations and the to-be-marketed formulation.

4. Question: *We would like to take this opportunity to confirm that the preclinical pharmacology studies outlined in Attachment 5 are sufficient to document that orally administered mesna does not effect the chemotherapeutic activity of ifosfamide.*

   At this time, Asta has provided adequate information.

ACTION ITEMS:

1. Asta is planning on submitting this NDA by 31 December 1996 and will include the US data.

2. Ms. Vaccari and Ms. Ryan will arrange for necessary communication regarding the specifics

of formatting the NDA for each discipline. The Agency's statistical guidance will be faxed as soon as available.

3. The PK study report on the requested study (#2 above) will be submitted by the sponsor no later than 2 months after submission of the proposed NDA.

There were no unresolved issues.

The meeting was concluded at 4:00 pm

/S/ 10-30-96
Project Manager

Concurrence /S/ 11/6/96
Robert Justice, M.D.
Deputy Director
Division of Oncology Drug Products

Attachment: Agenda - sponsor Overheads - sponsor Questions submitted by sponsor

cc:
Original IND — (with attachment)
HFD-150/Div File(with attachment)
HFD-150/RDeLap
HFD-150/GSokol
HFD-150/EMishina
HFD-150/WSchmidt
HFD-150/GChen
HFD-150 LVaccari(with attachment)
HFD-150/JJee
HFD-150/DPease

Drafted by: LVaccari/8-28-96
R/D init. by: EMishina/10-18-96
WSchmidt/9-8-96

Wp:minmtg/ —

MEMORANDUM OF MEETING - PreNDA Meeting

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-2375 FAX: (301) 594-0498

TO: Eileen Ryan (201) 525-2680
Asta Medica FAX (201) 488-8595

FROM: Leslie Vaccari, Project Manager 301-594-5778
Total number of pages, including cover sheet 4
Date: 1-7-97

COMMENTS:

Re: Minutes to Meeting of August 27, 1996

Please refer to attached pages.

Call me if I can be of further assistance.

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 20-855 Drug MESNEX (mesna) TABLETS DATE _____

Applicant Asta Medica CSO Taccari /Phone 594-5778

User Fee Goal Date: March 25, 1998

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP ____ AE ____ NA X N/A Yes ____ No ____
2. Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes X No ____
3. Completed copy of this CHECKLIST in package	Chem/Ther Types ____
4. LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	N/A Draft ____ Revised Draft ____ Final ____
5. PATENT INFORMATION	X
6. EXCLUSIVITY CHECKLIST	N/A
7. PEDIATRIC PAGE	N/A
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	X
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo expaining why.	X
10. REVIEWS:	
DIVISION DIRECTOR'S MEMO (If more than 1 review for any 1 discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented)	N/A
GROUP LEADER'S MEMO	N/A
MEDICAL REVIEW	✓ March 10 1998
SAFETY UPDATE REVIEW	✓ March 10 1998
STATISTICAL REVIEW	✓ March 3 1998
BIOPHARMACEUTICS REVIEW	✓ March 18 1998
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	✓ July 11, 1997
Statistical Review of Carcinogenicity Study(ies)	N/A
CAC Report/Minutes	N/A
CHEMISTRY REVIEW	✓ March 25 1998
Labeling and Nomenclature Committee Review Memorandum	✓ June 23, 1997
Date EER completed 2/20/98 (attach signed form or CIRTS printout) FUR needed ____ FUR requested ____	OK X No ____
Have the methods been validated?	Yes (attach) ____ No X
Environmental Assessment Review / FONSI	Review N/A FONSI N/A
MICROBIOLOGY REVIEW	N/A
What is the status of the monograph?	N/A
11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	X
12. MINUTES OF MEETINGS Date of End-of-Phase 2 Meeting — Date of pre-NDA Meeting Clinical 8-26-96 CMC Pre NDA 9-10-96	X
13. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes ____ Info Alert ____ Transcript ____ No mtg X
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	N/A
15. If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes ____ No X Yes, documentation attached ____ No, included in AP ltr X
16. INTEGRATED SUMMARY OF EFFECTIVENESS	X
17. INTEGRATED SUMMARY OF SAFETY	X

revision: 3/7/96

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

DA 20-855	Efficacy Supplement Type SE-	Supplement Number
Drug: Mesnes (mesna) Tablets		Applicant: Bristol-Myers Squibb / Baxter Oncology
RPM: Debra Vause	HFD-150	Phone # (301)594-5724
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	NA
• OC clearance for approval	NA
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
Exclusivity Summary (approvals only)	3/21/02
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	ODS 3/20/02

Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	3/20/02
• Most recent applicant-proposed labeling	3/20/02
• Original applicant-proposed labeling	8/20/01
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	Labeling Mtg: March 4, 11, & 12, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	3/20/02
• Reviews	3/19/02
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	NA
❖ Memoranda and Telecons	NA
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting NA	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA

[redacted]	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	3/20/02
❖ Clinical review(s) *(indicate date for each review)*	3/20/02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	3/20/02
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	3/20/02
❖ Statistical review(s) *(indicate date for each review)*	2/28/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	2/17/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	3/5/02
• Bioequivalence studies	3/5/02
[redacted]	
❖ CMC review(s) *(indicate date for each review)*	3/19/02, 3/20/02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	2/23/98
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	2/23/98
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
Facilities inspection (provide EER report)	Date completed: 9/10/01 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed Pending ( ) Requested ( ) Not yet requested
[redacted]	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	3/19/02
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

MESNA TABLETS

Application Summary

Foreign Marketing History

Mesna tablets are approved in the countries listed in Table 1. Marketing was initiated in the United Kingdom in October of 1995.

The text labeling which was approved in the UK is used in the other countries where mesna is approved with the exception of Germany. The German labeling differs from the labeling used in the other countries as outlined below:

- The indication is restricted to the cancer indications of the oxazaphosphorines (the class of drugs including ifosfamide and cyclophosphamide) Note:Use in autoimmune diseases was previously approved in Germany.
- Decreased kidney function is included in the contraindications
- Pediatric use: There is a statement that there is no experience in children
- Administration: this is limited to the intravenous plus oral route; the use of three oral doses is not included

A copy of the UK Package Insert and Patient Package Insert is included in this section.

Table 1 Countries in which Mesna Tablets are Approved for Marketing

Country	Approval Date
United Kingdom	March 1994
Denmark	September 1995
Netherlands	October 1996
Ireland	April 1996
Iceland	March 1996
Sweden	April 1996
Finland	October 1996
France	June 1996
Australia	July 1996
Belgium	August 1996
New Zealand	August 1996
Greece	September 1996
Germany	October 1996

10 pages redacted from this section of the approval package consisted of ~~draft~~ FOREIGN labeling

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#: D020134

DATE: March 18, 2002

FROM: Lauren Lee, Pharm.D.
Post-marketing Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

TO: Richard Pazdur, M.D., Director
Division of Oncology Drug Products, HFD-150

SUBJECT: OPDRA Post-marketing Safety Review

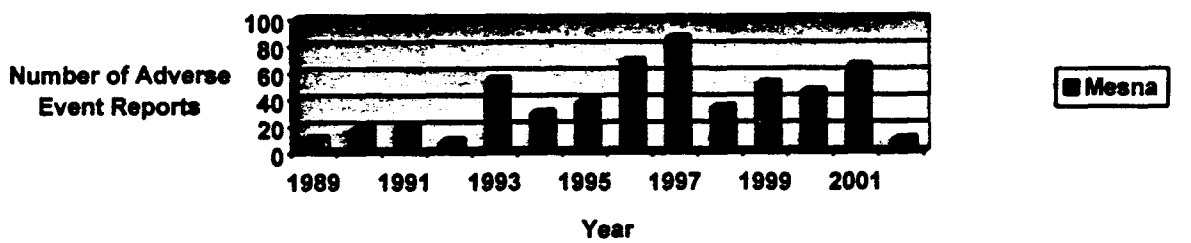
- Drugs: Mesnex (mesna)
  NDA 19-884, 20-855, [redacted] 19-763, 75-811, 75-764

This memo is in response to a consult request, by the Division of Oncology Drug Products, to review post-marketing adverse event data in AERS associated with the use of mesna and to provide any additional comment to the post-marketing surveillance portion of the proposed labeling. Mesnex (mesna injection) was first approved in the US on 12/30/1988. The NDA application for oral formulation is pending at this time.

As of March 13, 2002, there were 529 adverse event reports in AERS associated with mesna. However, since mesna is used in combination with ifosfamide or other chemotherapy regimens, it is difficult to distinguish adverse reactions which may be due to mesna from those caused by the concomitantly administered cytotoxic agents.

The following chart shows the number of reports received per year.

AERS Search Results



Reports by country are as follows:

Country	Reports	Country	Reports
United States	299	Denmark	4

France	63	Netherlands	6
Germany	45	Australia	2
Japan	30	Belgium	2
United Kingdom	17	Swaziland	2
Canada	11	Switzerland	2
Sweden	8	Finland	1

**This chart does not contain null cases that did not specify the country in which the adverse event was identified.*

Among all adverse event reports for mesna, the following are the most commonly reported adverse events. *[reported in at least 10 or more cases (per preferred term (PT) counts)]* Highlighted PT terms are unlabeled in the proposed package insert for mesna.

Preferred Terms (PT)	Count of PT's	Preferred Terms (PT)	Count of PT's
Pyrexia	96	Alanine Aminotransferase Increased	12
Leukopenia Nos	53	Anaemia Nos	12
Vomiting Nos	51	Atrial Fibrillation	12
Dyspnoea Nos	39	Blood Creatinine Increased	12
Sepsis Nos	38	Condition Aggravated	12
Hypotension Nos	27	Hypokalaemia	12
Encephalopathy Nos	26	Injection Site Reaction Nos	12
Confusion	24	Apnoea	11
Haematuria	24	Bone Marrow Depression Nos	11
Thrombocytopenia	24	Convulsions Nos	11
Hypersensitivity Nos	20	Cystitis Haemorrhagic	11
Neutropenia	20	Pain Nos	11
Diarrhoea Nos	19	Pruritus Nos	11
Tachycardia Nos	19	Rash Maculo-Papular	11
Dermatitis Nos	18	Rigors	11
Pneumonia Nos	18	Stupor	11
Pancytopenia	17	Urticaria Nos	11
Cardiac Arrest	16	Agitation	10
Nausea	16	Asthenia	10
Sedation	16	Chest pain	10
Dehydration	15	Coma	10
Hepatic Function Abnormal Nos	14	Erythema	10
Abdominal Pain Nos	13	Hallucination Nos	10
Headache Nos	13	Hypoxia	10
Medication Error	13	Pulmonary Oedema Nos	10
Renal Failure Nos	13	Vasodilation	10

Although most of the above unlabeled events may be related to other concomitant chemotherapy agents, the following 11 selected post-marketing adverse events were reviewed:

Sepsis (38), encephalopathy (26), neutropenia (20), pancytopenia (17), cardiac arrest(16), renal failure(13), atrial fibrillation (12), bone marrow depression (11), convulsion (11), coma (10), and pulmonary edema (10).

The reported cases for these events did not present any evidence to support that the reported events were directly related to mesna use. All of these events were possibly related to other concomitant chemotherapy agents or the progression of underlying disease. Further monitoring for additional cases is recommended. It is noteworthy, however, that the majority of the 26 encephalopathy cases (mostly foreign) cited ifosfamide as the likely cause for the adverse event *(Ifosfamide is not labeled for encephalopathy).* In five of these 26 reports, only ifosfamide and mesna (IV) were listed as suspect drugs, and unlike the remaining 21 reports, the use of other chemotherapeutic agents was not specified.

In addition to AERS searches, a Medline *(Pubmed)* internet search was conducted to retrieve any published literature case report of an adverse reaction possibly associated with the use of mesna (from years 1966-2000). One related article is presented below.

- Drug eruptions from mesna. After cyclophosphamide treatment of patients with systemic lupus erythromatosus and dermatomyositis *[Zonizits E, Tappeiner G,. Arch Dermatol 1992 Jan. 128(1);80-2.]*

  Drug eruptions to mesna have developed in 7 of 15 patients with autoimmune disorders treated with monthly pulses of intravenous cyclophosphamide. Two different types of drug eruptions were observed: five patients had development of a macular and partly papular or urticarial rash and angioedema and two patients had a generalized fixed drug eruption, primarily and predominantly at the sites of previous skin lesions of their underlying condition. The results of prick, patch, and intradermal tests were similar in both types of rash. However, the two patients with fixed drug eruption had developed a generalized eruption upon prick testing with mesna.

  These eruptions are not thought to share a common pathogenic mechanism. The results of skin and challenge tests do not support the hypothesis that a type 1 or a type 4 immune reaction may be responsible for these eruptions. The unusually high incidence (about 50%) of these reactions and their clinical presentation make it important to distinguish them from an exacerbation of the preexistent autoimmune disorder.

Given the above literature case and the fact that mesna has been shown to cause allergic reactions ranging from mild hypersensitivity to systemic anaphylactic reaction *(per labeling)*, a more thorough review of skin reactions is underway and will be sent to your Division at a later time.

In conclusion, based on the currently available information for mesna in the AERS database and in the medical literature, we concur with the proposed labeling at this time. *[See Appendix I for a brief summary of the proposed mesna labeling]*

S

Lauren Lee, Pharm.D.
Post-Marketing Safety Evaluator

Concur: S

Susan Lu, R.Ph.
Team Leader

cc: NDA 19-884, 20-855, [redacted] 19-763, 75-811, 19-884, 75-764
HFD-150: Pazdur/Martin/Vause

Electronic only cc:
HFD-430: Beitz/Lu/Lee/Guinn

D020134 MESNA/LEE/03/18/02

APPENDIX I

DRUG INFORMATION AND LABELING:

Drug Product	NDA	Applicant	FDA Approval	Dosage Forms	Strength	Reference Listed Product
Mesnex (mesna injection)	19-884	Asta	12/30/1988	Injectable	100 mg/ mL	Yes
Ifex/Mesnex Kit (ifosfamide and mesna injection)	19-763	Bristol Myers Squibb	10/10/1992	Injectable	100 mg/ mL	Yes
Mesna injection	75-811	Am Pharm Partners	4/26/2001	Injectable	100 mg/ mL	No
Mesna injection	75-764	Gensia Sicor Pharms	4/27/2001	Injectable	100 mg/ mL	No
Mesnex (mesna tablets)	20-855	Asta	Pending	Tablets	400 mg	Pending

Mesna is indicated as a prophylactic agent in reducing the incidence of ifosfamide induced hemorrhagic cystitis. Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna), and in the kidney, mesna disulfide reduces to free thiol compound which reacts chemically with the urotoxic ifosfamide metabolites resulting in their detoxification.

Mesna may be given on a fractionated dosing schedule of 3 bolus intravenous injections or a single bolus injection followed by 2 oral administrations of mesna tablets. Mesna may be given as intravenous bolus injections in a dosage equal to 20% of the ifosfamide dosage (w/w) at the time of ifosfamide administration and 4 and 8 hours after each dose of ifosfamide. The total daily dose of mesna is 60% of the ifosfamide dose.

Mesna injection may also be given as intravenous bolus injections in a dosage equal to 20% of the ifosfamide dosage (w/w) at the time of ifosfamide administration followed by mesna tablets orally in a dosage equal to 40% of the ifosfamide dose 2 and 6 hours after each dose of ifosfamide. The total daily dose of mesna is 100% of the ifosfamide dose. Patients who vomit within 2 hours of taking oral mesna should repeat the dose or receive intravenous mesna.

MESNEX PROPOSED LABELING (March 15, 2001)- *combined (IV/Oral) labeling*

Warnings: allergic reactions (ranging from mild hypersensitivity to systemic anaphylactic reactions)

Adverse Reactions:
Single doses of IV - headache, injection site reactions, flushing, dizziness, nausea, vomiting, somnolence, diarrhea, anorexia, fever, pharyngitis, hyperaesthesia, influenza-like symptoms, coughing

Single 1200 mg dose of an oral solution - rigors, back pain, rash, conjunctivitis, arthralgia

Tablets alone or IV followed by repeated doses of tablets – flatulence, rhinitis.
Repeated doses of IV – constipation

Global incidence of adverse events and incidence of most frequently reported adverse events in four controlled studies (IV and oral) - nausea, vomiting, constipation, leukopenia, fatigue, fever, anorexia,

thrombocytopenia, anemia, granulocytopenia, asthenia, abdominal pain, alopecia, dyspnea, chest pain, hypokalemia, diarrhea, dizziness, headache, pain, sweating increased, back pain, hematuria, injection site reaction, edema, edema peripheral, somnolence, anxiety, confusion, face edema, insomnia, coughing, dyspepsia, hypotension, pallor, dehydration, pneumonia, tachycardia, flushing

Postmarketing Surveillance: allergic reactions, decreased platelet counts associated with allergic reactions, hypertension, hypotension, increased heart rate, increased liver enzymes, injection site reactions (including pain and erythema), limb pain, malaise, myalgia, ST-segment elevation, tachycardia, tachypnea