CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-855

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-855

Bristol-Myers Squibb
Pharmaceutical Research Institute
Attention: Susan H. Behling
Director, Regulatory Science
Worldwide Regulatory Affairs
5 Research Parkway - P.O. Box 5100
Wallingford, CT 06492-7660

Dear Ms. Behling:

Please refer to your new drug application (NDA) dated September 20, 2001, received September 21, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesnex (mesna) Tablets.

We acknowledge receipt of your submissions dated August 24, 2001; September 24, and 27, 2001; October 2, 5, 8, 22, 25, and 29, 2001; February 13, and 22, 2002; March 4, and 12, 2002. Your submission of September 20, 2001 constituted a complete response to our March 25, 1998 action letter.

This new drug application provides for the use of Mesnex (mesna) Tablets as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on March 21, 2002.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-855." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We waived the pediatric study requirement for this action on this application on August 14, 2001.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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

If you have any questions, call Debra Vause, B.S.N., Regulatory Project Manager, at (301) 594-5724.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
3/21/02 11:53:06 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-855

Approvable Letter

MAR 25 1998

NDA 20-855

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

Attention: Aileen Ryan
Vice President, Regulatory Affairs and Compliance

Dear Ms. Ryan:

Please refer to your new drug application dated March 20, 1997, received March 25, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesnex (mesna) 400 mg Tablets.

We acknowledge receipt of your submissions dated May 16, July 29, August 19, September 17 and 19, October 10 and December 16, 1997, as well as January 30 and February 23, 1998. The User Fee goal date for this application is March 25, 1998.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. Serious deficiencies in your monitoring of the controlled U.S. study (D-07093-0018) have been identified by FDA's Division of Scientific Investigation (DSI). These new findings call into question the validity of the study results, which provided the critical urinary pharmacokinetic data upon which bioequivalence was based and also provided important safety information. Further DSI investigations are in progress.

2. The findings from the controlled U.S. study (D-07093-0018) did not achieve statistical equivalence when the data were re-analyzed using only first cycle data and excluding 12 patients from Center 5 (C. Julian Rosenthal) and 5 patients who discontinued from study prematurely.

Please submit a detailed description of your monitoring and auditing policies and actual practices over the course of this research, including a description of your current efforts to resolve monitoring deficiencies. We recommend that you re-audit all study records. The results of your re-auditing activities and DSI investigations will determine whether a new controlled clinical study comparing the proposed and currently approved mesna regimens will be needed.

We also have the following comments and requests for information that should be addressed:

1. A comparative pharmacokinetic study between the proposed IV plus oral dosing regimen and the approved IV dosing regimen evaluating the plasma and urinary pharmacokinetics of ifosfamide and mesna in the target population should be performed to address the following deficiencies and concerns. You should submit a protocol to the Agency for review.

   a. The multiple dose studies using the proposed IV plus oral dosing regimen suggested a larger systemic exposure of mesna and dimesna on Day 5 compared to that on Day 1. Therefore, the possible need for dose reduction after Day 1 should be assessed through further study.

   b. The plasma half-life of mesna in three of the five studies that attempted to define this parameter was different from the half life given in current labeling [redacted]

   c. The dissolution profiles of the to-be-marketed product manufactured at [redacted] differ from those of the products manufactured at [redacted] that were used in the pivotal trial.

2. No plasma protein binding study has been conducted. Only a publication which measured protein binding of radio-labeled mesna in rat serum was provided. Thus, a study to characterize human plasma protein binding of mesna should be conducted.

3. The following dissolution methodology and specification are recommended for 400 mg [redacted] film-coated mesna tablets:

Medium:	500 mL 0.06 N HCl at 37 ± 0.5°C
Apparatus:	USP Apparatus II (paddle) at 50 rpm
Specification:	Q = [redacted]% in 15 minutes

4. Comments on the process controls for the manufacture of mesna drug substance will be conveyed to [redacted] holder of DMF [redacted]

5. Please describe any [redacted] procedures, if used, for mesna drug substance, including the maximum time interval permitted.

6. It is proposed under impurities specifications for drug product that each unknown impurity should be no more than [redacted]%, and the sum of unknown impurities should be no more than [redacted]%. Individual impurities that are present to the extent of [redacted] % or greater should be monitored and structurally identified

in each batch, and the classification (e.g., starting material, intermediates, reactant, by-product, and degradation product, etc.) and the mode of formation of any of such impurities should be determined.

A tabulation should also be provided of the impurity analysis results of individual batches of drug substance and drug product, including those used in clinical, safety, and stability studies, and those representative of the product to be marketed.

Please refer to the 1997 ICH Quality Guidelines for Registration of Pharmaceuticals.

7. Please include degradation product (s) found, and [redacted] and [redacted] impurities in the Regulatory Specification and Methods for Drug Product.

8. The proposed specification for dimesna impurity in the drug product should be no more than [redacted]%. We believe this specification should be further tightened to [redacted]%, since the proposed new dosage form is a solid form. Please revise this specification or provide an explanation for the specification set.

9. The batch sizes for batches 608001, 608002, and 608003 submitted in the original submission, vol. 1.3, p 095 differ [redacted] from the information provided in your submission dated 5/16/97 page 4. Please clarify.

10. USP specifications and testing methods for average tablet weight, weight variation and disintegration tests for Mesnex Tablets should be followed or equivalency should be demonstrated for other methods.

11. Please explain the origin of [redacted] listed in the stability tests and specifications. The chemical structure of this compound should be identified, since it is found at a level greater than [redacted]%. Please see comment No. 6 for further detail.

12. In the stability report, the regulatory specifications should be given for Mesnex tablets and the date of each test interval. The identification test, residual solvents, sum of unknown impurities, and weight variation are not included in your stability report as listed in ASTA Medica, Test Specification for Stability Studies, Vol. 1.3 p 166.

13. The impurities, [redacted] should be included in your stability report for Mesnex Tablets as well as any degradants found. The Dissolution test specifications should be changed to:

Medium: 500 mL 0.06 N HCl at 37 ± 0.5 °C
Apparatus: USP Apparatus II (paddle) at 50 rpm
Specification: Q=[redacted]% in 15 minutes

14. Please provide ASTA procedures for failed batches of Mesnex Tablets and describe the rework procedures.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Patrick Guinn, Project Manager, at (301) 827-1537.

Sincerely yours,

/S/ 3/25/98

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-855
HFD-150/Div. files
HFD-002/ORM
HFD-101/Office Director
HFD-810/ONDC Division Director
DISTRICT OFFICE
HFD-92/DDM-DIAB
HFD-150/PGuinn
HFD-150/RDeLap
HFD-150/RJustice
HFD-150/JBeitz
HFD-150/GSokol
HFD-150/RWood
HFD-150/JJee
HFD-150/PAndrews
HFD-150/WSchmidt
HFD-150/ARahman
HFD-150/JDuan
HFD-150/TKoutsoukos
HFD-150/GChen
HFD-150/DPease
HFD-150/LVaccari

Drafted by: PGuinn/March 23, 1998

Initialed by: DPease/3-23-98
WSchmidt/3-24-98
PAndrews/3-23-98
GChen/3-23-98
TKoutsoukos/3-23-98
JDuan/3-23-98
ARahman/3-23-98
JJee/3-23-98
RWood/3-23-98
GSokol/3-23-98
JBeitz/3-24-98
RDeLap/3-24-98

F/T by: PGuinn/3-25-98
final init. by: DPease/ (S) 3-25-98

NOT APPROVABLE (NA)

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_____ pages redacted from this section of the approval package consisted of draft labeling