CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-764

Generic Name: Mesna Injection, 100 mg/mL

Sponsor: Gensia Sicor Pharmaceuticals, Inc.

Approval Date: April 27, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-764

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-764

APPROVAL LETTER

ANDA 75-764

APR 27 2001

Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
19 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application dated December 22, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Mesna Injection, 100 mg/mL (packaged in 10 mL multiple-dose vials).

Reference is also made to your amendments dated September 18, 2000, and March 29, and April 26, 2001.

The listed drug referenced in your application, Mesnex Injection of Asta Pharma AG, is subject to a period of patent protection which expires on October 6, 2013 (U.S. Patent No. 5,696,172). We note that required information on this patent was not submitted to the agency in a timely manner as required under 21 CFR 314.94(a)(12)(vi). Therefore, Gensia-Sicor Pharmaceuticals, Inc. is not required to submit an amended patent certification to address this patent. We note that your April 26, 2001, amendment provided for the withdrawal of your "Paragraph IV Certification" to the '172 patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Mesna Injection, 100 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Mesnex® Injection, 100 mg/mL, of Asta Pharma AG).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.
We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies, which may be identified.

Sincerely yours,

/S/

4/27/2001

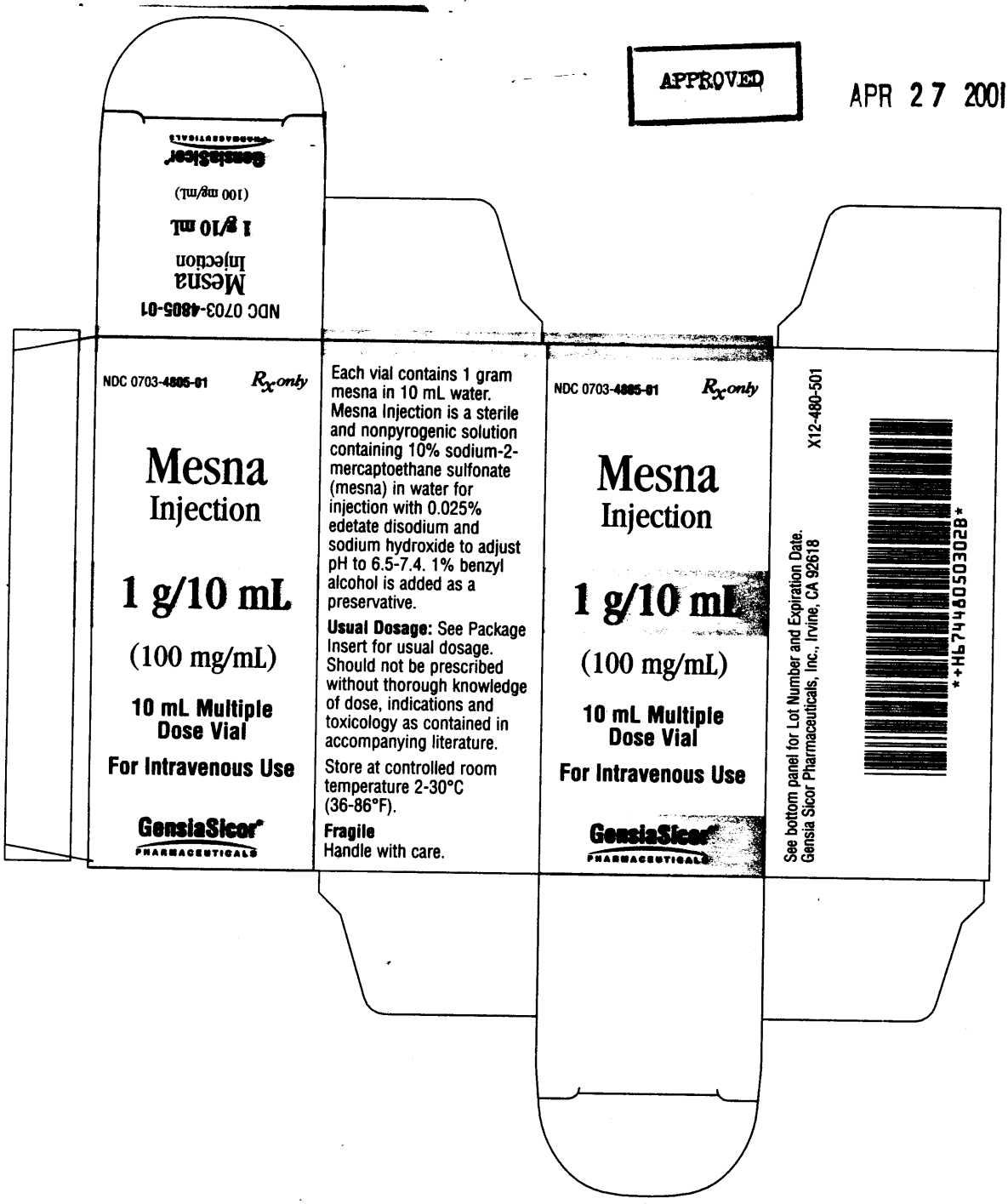
Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-764

Final Printed Labeling



APPROVED

APR 27 2001

NDC 0703-4805-01

Mesna
Injection

1 g/10 mL

(100 mg/mL)

GensiaSicor PHARMACEUTICALS

NDC 0703-4805-01 R_x only

Mesna
Injection

1 g/10 mL

(100 mg/mL)

10 mL Multiple Dose Vial

For Intravenous Use

GensiaSicor PHARMACEUTICALS

Each vial contains 1 gram mesna in 10 mL water. Mesna Injection is a sterile and nonpyrogenic solution containing 10% sodium-2-mercaptoethane sulfonate (mesna) in water for injection with 0.025% edetate disodium and sodium hydroxide to adjust pH to 6.5-7.4. 1% benzyl alcohol is added as a preservative.

Usual Dosage: See Package Insert for usual dosage. Should not be prescribed without thorough knowledge of dose, indications and toxicology as contained in accompanying literature.

Store at controlled room temperature 2-30°C (36-86°F).

Fragile
Handle with care.

NDC 0703-4805-01 R_x only

Mesna
Injection

1 g/10 mL

(100 mg/mL)

10 mL Multiple Dose Vial

For Intravenous Use

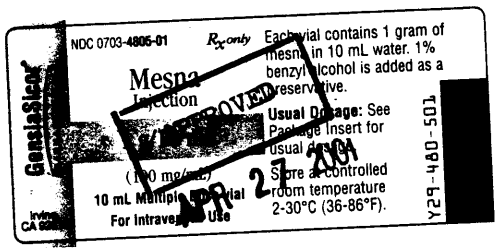
GensiaSicor PHARMACEUTICALS

X12-480-501

See bottom panel for Lot Number and Expiration Date.
Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618

+H67448050302B

VIAL LABEL/SHELF PACK A LABEL
Part #Y29-480-501



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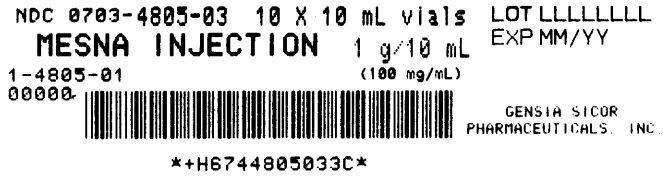
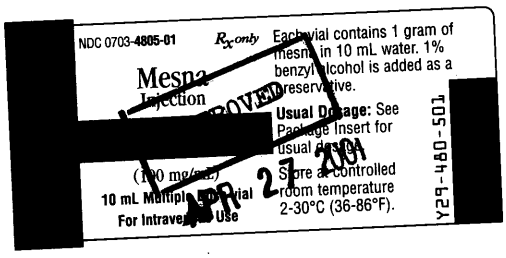


VIAL LABEL/SHELF PACK A LABEL
Part #Y29-480-501



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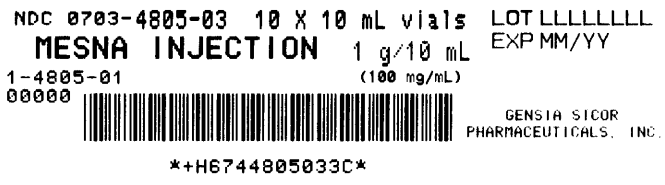


Y36-999-551
Package Insert

GensiaSicor® PHARMACEUTICALS

R_x only

Mesna Injection

APPROVED

APR 27 2001

DESCRIPTION

Mesna injection is a detoxifying agent to inhibit the hemorrhagic cystitis induced by ifosfamide. The active ingredient mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$ and a molecular weight of 164.18. Its structural formula is as follows:

$$HS\text{-}CH_2\text{-}CH_2SO_3^-Na^+$$

Mesna injection is a sterile, nonpyrogenic, aqueous solution of clear and colorless appearance in flint glass multiple dose vials for intravenous administration. Mesna injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium, sodium hydroxide for pH adjustment and 10.4 mg of benzyl alcohol as a preservative. The solution has a pH range of 6.5-7.4.

CLINICAL PHARMACOLOGY

Mesna was developed as a prophylactic agent to prevent the hemorrhagic cystitis induced by ifosfamide. Analogous to the physiological cysteine-cystine system, following intravenous administration, mesna is rapidly oxidized to its only metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys.

In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and other urotoxic metabolites.

After administration of an 800 mg dose the half-lives of mesna and dimesna in the blood are 0.36 hours and 1.17 hours respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna has a volume of distribution of 0.652 L/kg and a plasma clearance of 1.23 L/kg/hour. Ifosfamide has been shown to have dose dependent pharmacokinetics in humans. At doses of 2-4 g, its terminal elimination half-life is about 7 hours. As a result, in order to maintain adequate levels of mesna in the urinary bladder during the course of elimination of the urotoxic ifosfamide metabolites, repeated doses of mesna are required.

Based on the pharmacokinetic profiles of mesna and ifosfamide as discussed above, mesna was given as bolus doses prior to ifosfamide and at 4 and 8 hours after ifosfamide administration. The hemorrhagic cystitis produced by ifosfamide is dose dependent. At a dose of 1.2 g/m² ifosfamide administered daily for 5 days, 16% to 26% of the patients who received conventional uroprophylaxis (high fluid intake, alkalinization of

the urine and the administration of diuretics) developed hematuria (>50 rbc/hpf or macrohematuria). In contrast, none of the patients who received mesna together with this dose of ifosfamide developed hematuria. Higher doses of ifosfamide from 2 to 4 g/m^2 administered for three to five days, produced hematuria in 31 to 100% of the patients. When mesna was administered together with these doses of ifosfamide the incidence of hematuria was less than 7%.

INDICATIONS AND USAGE

Mesna has been shown to be effective as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.

CONTRAINDICATIONS

Mesna is contraindicated in patients known to be hypersensitive to mesna or other thiol compounds.

WARNINGS

Allergic reactions to mesna were reported in patients with autoimmune disorders. The majority of the patients received high doses of mesna orally. The symptoms ranged from mild hypersensitivity to systemic anaphylactic reactions.

Mesna has been developed as an agent to prevent ifosfamide induced hemorrhagic cystitis. It will not prevent or alleviate any of the other adverse reactions or toxicities associated with ifosfamide therapy.

Mesna does not prevent hemorrhagic cystitis in all patients. Up to 6% of patients treated with mesna have developed hematuria (>50 rbc/hpf or WHO grade 2 and above). As a result, a morning specimen of urine should be examined for the presence of hematuria (red blood cells) each day prior to ifosfamide therapy. If hematuria develops when mesna is given with ifosfamide according to the recommended dosage schedule, depending on the severity of the hematuria, dosage reductions or discontinuation of ifosfamide therapy may be initiated.

In order to obtain adequate protection, mesna must be administered with each dose of ifosfamide as outlined in the **DOSAGE AND ADMINISTRATION** section. Mesna is not effective in preventing hematuria due to other pathological conditions such as thrombocytopenia.

Because of the benzyl alcohol content, the multiple dose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

PRECAUTIONS

Laboratory Tests

A false positive test for urinary ketones may arise in patients treated with mesna. In this test, a red-violet color develops which, with the addition of glacial acetic acid, will return to violet.

Pediatrics

Because of the benzyl alcohol content, the multiple dose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

Drug Interactions

In vitro and *in vivo* animal tumor models have shown that mesna does not have any effect on the antitumor efficacy of concomitantly-administered cytotoxic agents.

Carcinogenesis, Mutagenesis and Impairment of Fertility

No long term animal studies have been performed to evaluate the carcinogenic potential of mesna. The Ames Salmonella typhimurium test, mouse micronucleus assay and frequency of sister chromatid exchange and chromosomal aberrations in PHA-stimulated lymphocytes *in vitro* assays revealed no mutagenic activity.

Pregnancy

Pregnancy Category B. Reproduction studies in rats and rabbits with oral doses up to 1000 mg/kg have revealed no harm to the fetus due to mesna. It is not known whether mesna can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Mesna should be given to a pregnant woman only if the benefits clearly outweigh any possible risks.

Teratology studies in rats and rabbits have shown no effects.

Nursing Mothers

It is not known whether mesna or dimesna is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from mesna, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

Because mesna is used in combination with ifosfamide and other chemotherapeutic agents with documented toxicities, it is difficult to distinguish the adverse reactions which may be due to mesna from those caused by the concomitantly administered cytostatic agents. As a result, the adverse reaction profile of mesna was determined in three Phase I studies (16 subjects) utilizing intravenous and oral administration and two controlled studies in which ifosfamide and mesna were compared to ifosfamide and standard prophylaxis.

In Phase I studies in which IV bolus doses of 0.8-1.6 g/m^2 mesna were administered as single or three repeated doses to a total of 10 patients, a bad taste in the mouth (100%) and soft stools (70%) were reported. At intravenous and oral bolus doses of 2.4 g/m^2 which are approximately 10 times the recommended clinical doses (0.24 g/m^2) headache (50%), fatigue (33%), nausea (33%), diarrhea (83%), limb pain (50%), hypotension (17%) and allergy (17%) have also been reported in the 6 patients who participated in this study.

In controlled clinical studies, adverse reactions which can be reasonably associated with mesna were vomiting, diarrhea and nausea.

OVERDOSAGE

There is no known antidote for mesna.

DOSAGE AND ADMINISTRATION

For the prophylaxis of ifosfamide induced hemorrhagic cystitis, mesna may be given on a fractionated dosing schedule of bolus intravenous injections as outlined below.

Mesna is 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.

The recommended dosing schedule is outlined below:

	0 Hours	4 Hours	8 Hours
Ifosfamide	1.2 g/m²	—	—
Mesna	240 mg/m²	240 mg/m²	240 mg/m²

In order to maintain adequate protection, this dosing schedule should be repeated on each day that ifosfamide is administered. When the dosage of ifosfamide is adjusted (either increased or decreased), the dose of mesna should be modified accordingly. When exposed to oxygen, mesna is oxidized to the disulfide, dimesna.

The mesna multiple dose vials may be stored and used for up to 8 days.

PREPARATION OF INTRAVENOUS SOLUTIONS/STABILITY

For IV administration the drug can be diluted by adding the mesna injection solution to any of the following fluids obtaining final concentrations of 20 mg mesna/mL fluid:

5% Dextrose Injection, USP
5% Dextrose and 0.2% Sodium Chloride Injection, USP
5% Dextrose and 0.33% Sodium Chloride Injection, USP
5% Dextrose and 0.45% Sodium Chloride Injection, USP
0.92% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP

For example:

One mL of mesna injection multiple dose vial 100 mg/mL may be added to 4 mL of any of the solutions listed above to create a final concentration of 20 mg mesna/mL fluid.

Diluted solutions are chemically and physically stable for 24 hours at 25°C (77°F).

Mesna is not compatible with cisplatin.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

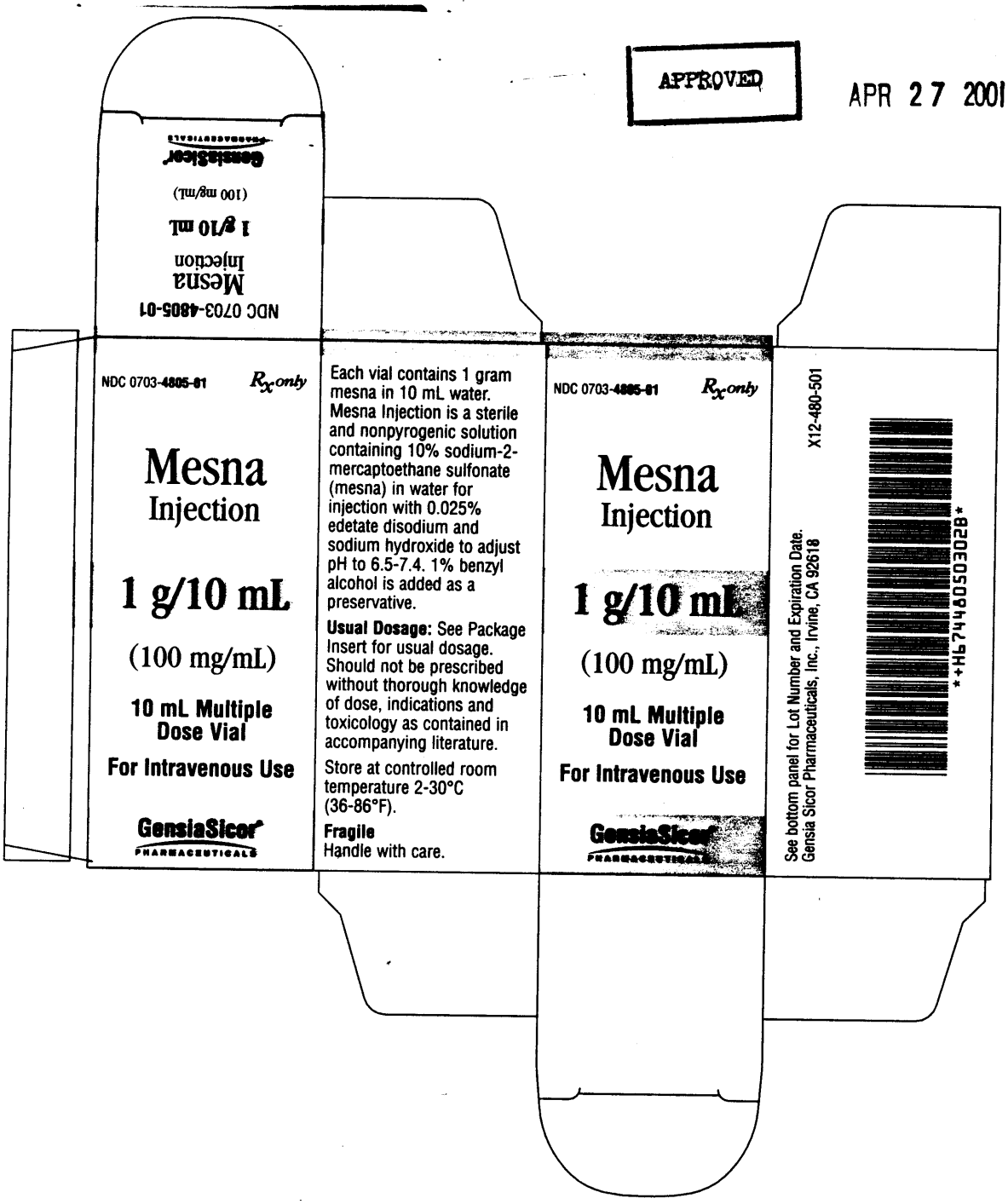
HOW SUPPLIED

Mesna injection is available as follows:

NDC Number	Concentration	Package Size
0703-**4805-03**	100 mg/mL	10 mL vials packaged 10 per shelf pack

Store at controlled room temperature 2-30°C (36-86°F).

Issued: July 2000
Gensia Sicor Pharmaceuticals, Inc.
Irvine, CA 92618



APPROVED

APR 27 2001

NDC 0703-4805-01

Mesna
Injection

1 g/10 mL

(100 mg/mL)

GensiaSicor PHARMACEUTICALS

NDC 0703-4805-01 R_x only

Mesna
Injection

1 g/10 mL

(100 mg/mL)

10 mL Multiple Dose Vial

For Intravenous Use

GensiaSicor PHARMACEUTICALS

Each vial contains 1 gram mesna in 10 mL water. Mesna Injection is a sterile and nonpyrogenic solution containing 10% sodium-2-mercaptoethane sulfonate (mesna) in water for injection with 0.025% edetate disodium and sodium hydroxide to adjust pH to 6.5-7.4. 1% benzyl alcohol is added as a preservative.

Usual Dosage: See Package Insert for usual dosage. Should not be prescribed without thorough knowledge of dose, indications and toxicology as contained in accompanying literature.

Store at controlled room temperature 2-30°C (36-86°F).

Fragile
Handle with care.

NDC 0703-4805-01 R_x only

Mesna
Injection

1 g/10 mL

(100 mg/mL)

10 mL Multiple Dose Vial

For Intravenous Use

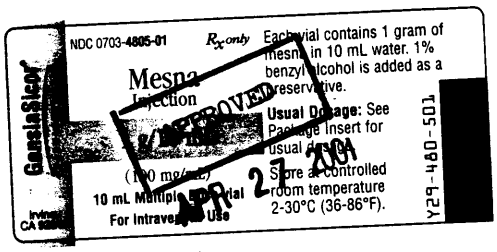
GensiaSicor PHARMACEUTICALS

X12-480-501

See bottom panel for Lot Number and Expiration Date.
Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618

+H6744050302B

VIAL LABEL/SHELF PACK A LABEL
Part #Y29-480-501



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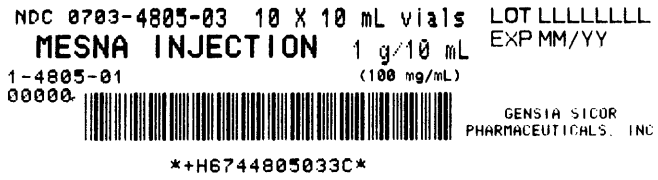
Part #1-4805-01



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-764

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-764

3. NAME AND ADDRESS OF APPLICANT

Gensia Sicor Pharmaceuticals, Inc.
19 Hughes
Irvine, CA 92618

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that, in its opinion and to the best of its knowledge, patent #4220660 held by Asta Pharma AG will expire on 3/6/2001 and no marketing exclusivities exist for Asta Pharma AG's Mesnex.

5. SUPPLEMENT(s)

Original 12/22/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Mesna Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

10. PHARMACOLOGICAL CATEGORY
uroprotective

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF's 3880, 1546

13. DOSAGE FORM

Liquid

14. POTENCY

100 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Sodium 2-mercaptoethane sulfonate

16. RECORDS AND REPORTS

17. COMMENTS

[

]

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 6/5/00

Supervisor: Paul Schwartz, Ph.D.

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1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-764

3. NAME AND ADDRESS OF APPLICANT

Gensia Sicor Pharmaceuticals, Inc.
19 Hughes
Irvine, CA 92618

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that, in its opinion and to the best of its knowledge, patent #4220660 held by Asta Pharma AG will expire on 3/6/2001 and no marketing exclusivities exist for Asta Pharma AG's Mesnex. Filed Paragraph IV certification for patent 172.

5. SUPPLEMENT(s)

Original 12/22/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Mesna Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Paragraph IV 9/14/00
Amendment 9/18/00
Amendment 11/3/00 patent Amendment, notification of patent infringement lawsuit
Amendment 3/29/01 - Minor revisions to the analytical methods.

10. PHARMACOLOGICAL CATEGORY
uroprotective

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF's —

13. DOSAGE FORM

Liquid

14. POTENCY

100 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Sodium 2-mercaptoethane sulfonate

16. RECORDS AND REPORTS

17. COMMENTS

The microbiology portion of the application is satisfactory 3/28/01.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable, but firm has been sued by innovator.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 4/3/01

Supervisor: Paul Schwartz, Ph.D. 4/6/01

cc: ANDA 75-764
Dup
Div File

Endorsements:

/S/ 4/11/01
HFD-627/NNashed/

HFD-627/PSchwartz/ /S/ 4/11/01

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F/T by: DJ 4/10/01

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-764

MICROBIOLOGY REVIEW

Office of Generic Drugs, HFD-620
Microbiology Review #1
June 26, 2000

A. 1. **ANDA:** **75-764**

APPLICANT: Gensia Sicor Pharmaceuticals, Inc.
19 Hughes
Irvine, CA 92618-1902

2. PRODUCT NAME: Mesna Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 100 mg/mL as a 10-mL fill in a 10-mL multiple-dose vial; Intravenous injection

4. METHOD OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: antidote for ifosfamide (anti-neoplastic)

B. 1. DATE OF INITIAL SUBMISSION: December 22, 1999; Received Dec. 23, 1999

Subject of this Review

2. DATE OF AMENDMENT: no amendments related to sterility assurance

3. RELATED DOCUMENTS:
DMF [redacted]
DMF [redacted]

4. ASSIGNED FOR REVIEW: June 20, 2000

C. REMARKS: The subject drug product is manufactured at the Gensia Sicor facility in Irvine, California; the drug product is filled into vials on Filling Line #2.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] process are provided in "E. REVIEW NOTES" and "MICROBIOLOGY COMMENTS TO BE PROVIDED TO THE APPLICANT" found at the end of this review. The deficiencies noted represent **Minor Deficiencies**.

/S/ 6/29/2000
Paul C. DeLeo, Ph.D.

/S/ 6/29/00

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Division Copy
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Drafted by P. DeLeo, HFD-600; V:\MICROREV\75764MR1.DOC
Initialed by A. High

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Office of Generic Drugs, HFD-620
Microbiology Review #2
March 27, 2001

A. 1. **ANDA:** 75-764

APPLICANT: Gensia Sicor Pharmaceuticals, Inc.
19 Hughes
Irvine, CA 92618-1902

2. PRODUCT NAME: Mesna Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 100 mg/mL as a 10-mL fill in a 10-mL multiple-dose vial; Intravenous injection

4. METHOD OF STERILIZATION: [redacted] **followed by** [redacted]

5. PHARMACOLOGICAL CATEGORY: antidote for ifosfamide

B. 1. DATE OF INITIAL SUBMISSION: December 22, 1999;

2. DATE OF AMENDMENT: September 18, 2000
Subject of this Review (Recd. September 19, 2000)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: March 26, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated July 10, 2000.

D. CONCLUSIONS: The submission is **recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] process are provided in "E. REVIEW NOTES".

/S/ 3/28/01
Nrapendra Nath, Ph.D.
/S/ 3/28/01

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Initialed by A. High

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-764

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

GENERIC NAME: **Mesna** ANDA # : 75-764
SPONSOR: **Gensia Sicor Pharmaceutical**
DOSAGE FORM: Injection
STRENGTH(S): 100 mg/ml
TYPES OF STUDIES: NA
CLINICAL STUDY SITE(S): NA
ANALYTICAL SITE(S): NA

STUDY SUMMARY : NA

Waiver request is granted.

DISSOLUTION : NA

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility NA For cause NA Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Nhan T. Tran, Ph.D.
INITIAL : /S/ BRANCH: II
DATE : 3/7/00

TEAM LEADER : Shriniwas Nerurkar, Ph.D.
INITIAL : /S/ BRANCH: II
DATE : 3/7/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : /S/ DATE : 3/16/00

Mesna Injection
100 mg/ml
AADA # 75-764
Reviewer: Nhan L. Tran

Gensia Sicor
Irvine, CA
Submission Date:
December 22, 1999

Review of a Waiver Request

Background:

Mesna injection is indicated for the prevention of the hemorrhagic cystitis induced by ifosfamide. The reference listed drug is Mesnex^{R}, manufactured by Asta Pharma AG. The present submission, **ANDA 75-764,** mesna injection, 100 mg/ml in 10 ml vial, is for intravenous use only.
The firm cited the following provisions of 21 CFR 320.22 (b)(1) to support the waiver request.

1. The test product is a parenteral solution intended solely for intravenous administration; and

2. The test product contains the same active and inactive ingredients, in the same concentration as Mesnex^{R}, manufactured by Asta Pharma AG (NDA #19-884).

COMPARATIVE COMPOSITIONS (Not to be released under FOI):

Ingredient	*Test*	*Reference*
	Amount/ml	
Mesna	100.0 mg	100.0 mg
Edetate Disodium	0.250 mg	0.250 mg
Benzyl alcohol	10.4 mg	10.4 mg
Sodium Hydroxide	pH adjustment	pH adjustment
Water For Injection	QS	QS

Comment:

The test and reference products contain the same active and inactive ingredients, in the same dosage form and route of administration as the reference listed drug.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Gensia Sicor demonstrates that its Mesna injection, 100 mg/ml falls under 21 CFR Section 320.22(1) of Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study requirements for Mesna 100mg/mL of the test product is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Mesnex® injection 100mg/mL manufactured by Asta Pharma AG.

/S/

Nhan L. Tran
Division of Bioequivalence

/S/ 3/7/00

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

CONCUR: /S/ Date: 3/16/00

Dale P. Conner, Pharm.D
Director, Division of Bioequivalence.

cc: AADA # 75-764 (original), HFD-655 (Tran, Nerurkar), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS

ANDA: 75-764 APPLICANT: Gensia Sicor

DRUG PRODUCTS: Mesna injection, 100 mg/mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet, and has the following comment:

The Division of Bioequivalence agrees that information submitted demonstrates that your Mesna 100mg/ml for intravenous administration (IV) falls under 21 CFR Section 320.22(1) of Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study requirements for the products is granted.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA: 75-764
DIVISION FILE

DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer
HFD-655/Bio Team Leader /S/ 3/20/00
HFD-617/Project Manager /S/
HFD-650/Dale Conner /S/ 3/16/00

WAIVER (WAI) Submission Date: **December 22, 1999**
Strengths: 100 mg/ml

Outcome: **AC**

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-764

ADMINISTRATIVE DOCUMENTS

1.1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-764 **Date of Submission: December 22, 1999**
Applicant's Name: Gensia Sicor
Established Name: Mesna Injection, 100 mg/mL

Labeling Deficiencies:

1. CONTAINER (10 mL) – Satisfactory in draft.

2. CARTON (1 x 10 mL) – Satisfactory in draft.

3. SHELF PACK LABEL (10 individual cartons/shelf pack) – Satisfactory in draft.

4. INSERT – Satisfactory in draft.

Please submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels:
Carton Labeling:
Professional Package Insert Labeling:
Revisions needed post-approval:
BASIS OF APPROVAL:
Was this approval based upon a petition? Yes No
What is the RLD on the 356(h) form: MESNEX®
NDA Number: 19-884/S-005
NDA Drug Name: Mesna Injection, 100 mg/mL
NDA Firm: Asta Medica
Date of Approval of NDA Insert and supplement #: September 25, 1995
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side by side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side by side comparison with innovator labeling in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	X		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug for this product is MESNEX®(Asta Medica; NDA#19-884/S-005; Approved September 25, 2995).
2. There is one patent in effect: PATENT#4220660 – U-21- For treatment of humans suffering undesired urotoxic side effects caused by cytostatically active alkylating agents. Expires: March 6, 2001. The firm certifies that it will not market until after the expiration date. See Vol. 1.1, page 12.
3. The product is manufactured by Gensia Sicor 19 Hughes, Irvine, CA 92618-1902. See Vol. 1.1,page 114.
4. No outside firms are utilized. See Vol. 1.1, page 117.
5. Container/Closure:
   Vial: 10 mL
   Stopper
   Overseal:
   See Vol. 1.1, page 269.
6. Finished Product: clear colorless aqueous solution. See Vol. 1.1, page 28.

7. Product line: 10 mL vials in shelf packs of ten. See Vol. 1.1, page 29.
8. Components/Composition
   Innovator:
   Active: Mesna 100 mg/mL
   Inactive: edetate disodium 0.25 mg/mL
   Sodium hydroxide to adjust pH
   Multidose vials only- 10.4 mg benzyl alcohol as a preservative.
   Applicant:
   Active: Mesna, 100 mg/mL
   Inactive: Edetate disodium, 0.25 mg
   Benzyl Alcohol, 10.4 mg
   Water for injection, q.s.
   Sodium hydroxide to adjust pH

   See Vol. 1.1, page 36.
9. Storage/Dispensing
   NDA: Store at controlled room temperature 15-30°C (59-86°F).
   ANDA: Store at controlled room temperature 15-30°C (59-86°F).
   See Vol. 1.1, page 29.

Date of Review: February 17, 2000
Date of Submission: December 22, 2000

Reviewer: /S/ **Date:** 2/23/2000

Team Leader: /S/ **Date:** 2/24/2000

cc:
NDA: 75-764
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSAM\GENSIA\LTRS&REV\75764na1.l
Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-764 **Date of Submission: December 22, 1999**
Applicant's Name: Gensia Sicor
Established Name: Mesna Injection, 100 mg/mL

Labeling Deficiencies:
1. CONTAINER (10 mL) – Satisfactory in draft.

2. CARTON (1 x 10 mL) – Satisfactory in draft.

3. SHELF PACK LABEL (10 individual cartons/shelf pack) – Satisfactory in draft.

4. INSERT – Satisfactory in draft.

Please submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-764 **Date of Submission: September 18, 2000**

Applicant's Name: Gensia Sicor

Established Name: Mesna Injection, 100 mg/mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: Satisfactory as of September 18, 2000 submission.
Carton Labeling: Satisfactory as of September 18, 2000 submission.
Professional Package Insert Labeling: Satisfactory as of September 18, 2000 submission.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: MESNEX®
NDA Number: 19-884/S-005
NDA Drug Name: Mesna Injection, 100 mg/mL
NDA Firm: Asta Medica
Date of Approval of NDA insert and supplement #: September 25, 1995
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side by side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side by side comparison with innovator labeling in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			

Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	X		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug for this product is MESNEX®(Asta Medica; NDA#19-884/S-005; Approved September 25, 1995).
2.

No	Expiration	Use code	Use	File
5696172	Oct. 6, 2013		Injectable mesna solutions having a pH value higher than 7.5. The solutions have increased storage stability	P-IV
4220660	March 6, 2001	U-21	For treatment of humans suffering undesired urotoxic side effects caused by cytostatically active alkylating agents	P-III

3. The product is manufactured by Gensia Sicor 19 Hughes, Irvine, CA 92618-1902. See Vol. 1.1,page 114.
4. No outside firms are utilized. See Vol. 1.1, page 117.
5. Container/Closure: Vial: 10 mL
   Overseal: See Vol. 1.1, page 269.
6. Finished Product: clear colorless aqueous solution. See Vol. 1.1, page 28.
7. Product line: 10 mL vials in shelf packs of ten. See Vol. 1.1, page 29.
8. Components/Composition
   Innovator:
   Active: Mesna 100 mg/mL
   Inactive: edetate disodium 0.25 mg/mL, Sodium hydroxide to adjust pH, Multidose vials only- 10.4 mg benzyl alcohol.
   Applicant:
   Active: Mesna, 100 mg/mL
   Inactive: Edetate disodium, 0.25 mg, Benzyl Alcohol, 10.4 mg, Water for injection, q.s., Sodium hydroxide to adjust pH. See Vol. 1.1, page 36.
9. Storage/Dispensing
   NDA: Store at controlled room temperature 15-30°C (59-86°F).
   ANDA: Store at controlled room temperature 15-30°C (59-86°F). See Vol. 1.1, page 29.
10. In order to avoid infringing on patent 5696172 (see above), the firm has revised the pH of its formulation to be 6.5 to 7.4 rather than 6.5 to 8.5. See Vol. 1.1, page 26 of September 18, 2000 submission.

Date of Review: September 26, 2000 **Date of Submission: September 18, 2000**

Reviewer: /S/ **Date:** 9/26/00

Team Leader: /S/ **Date:** 10/10/2000

cc:

ANDA 75-764
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSAM\GENSIA\LTRS&REV\75764NA2.I
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-764

CORRESPONDENCE

FILE IN ANDA 75-764

M E M O R A N D U M

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

DATE: April 24, 2001

FROM: Robert L. West, Acting Deputy Director
Office of Generic Drugs

/S/ 4/24/01

SUBJECT: PATENT AND FORMULATION ISSUES ASSOCIATED WITH NDA 19-884 FOR MESNEX (Mesna) INJECTION

THROUGH: Frank Holcombe, Jr., Ph.D.
Associate Director for Chemistry
Office of Generic Drugs

/S/ 4/24/01

Mary Fanning, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

/S/ 4/26/01

Elizabeth Dickinson
Office of Chief Counsel

OK per /S/

TO: The Record for ANDA 75-811 for American Pharmaceutical Partners (APP) Mesna Injection 100 mg/mL, 10 mL vials

On July 5, 2000, Asta Pharma AG (Asta), the holder of the NDA 19-884 for Mesnex (Mesna) Injection submitted a Special Supplement - Changes Being Effected to provide for a change in the finished product specification for the pH range for Mesnex. Asta stated that the newly proposed pH range (7.5 - 8.5) would provide for increased stability of the drug product and would justify extending the expiration period for the drug product from 2 years to 3 years. The supplement was approved on July 26, 2000.

According to Asta, the previously approved pH range was 6.5 - 8.5 for Mesnex packaged in 2 mL single-dose ampules and 7.0 - 8.0 for Mesnex packaged in 10 mL multiple-dose vials. Mesnex previously had a 2-year expiration date.

ANDA 75-811 submitted by American Pharmaceutical Partners (APP) has a finished product specification for pH of 6.5 - 8.5, a range that is within the previously approved range for Mesna. In addition, APP has requested a 2-year expiration date based upon data from accelerated stability studies and has adequate controls in place to monitor for increases in impurity levels.

It is our finding that there are no safety issues associated with APP's proposed specification for pH. This is the same specification which was previously approved for the reference listed drug, Mesna. Asta Pharma proposed a more restrictive pH range in order to justify a 3 year expiration dating period for Mesna. APP has in place adequate controls to assure that the finished drug product's identity, strength, purity, and quality of its product remain within the specifications

which are proposed for approval throughout its labeled 2 year expiration dating period.

Changes in specifications of the type noted above are permitted in abbreviated new drug applications. Finished product specifications often differ between those proposed by the manufacturer of the generic drug product and those that which have been approved for the NDA holder. The agency does not expect that all manufacturers will follow the exact same manufacturing process since certain processes are proprietary and may be protected by patents. Each ANDA applicant must include a section in their application to which they describe in detail the chemistry manufacturing process and the controls they have established to assure drug quality (21 CFR 314.94(a)(9) and 314.50(d)(1). Differences between the generic and reference products occurring as a result of different manufacturing processes (such as a change in the pH range) are permitted to be included in the labeling of the generic product (21 CFR 314.94(a)(8)(iv).

In addition, Asta Medica submitted a new patent, U.S. Patent No. 5,696,172, expiring on October 6, 2013, for inclusion in the Orange Book for Mesna. Asta's stated in a August 3, 2000 submission that this patent applies to the drug product that is the subject of the supplemental application referenced above. The declaration included with the patent states that the patent "cover(s) the formulation, composition, and/or method of use of Mesnex (Mesna) Injection as modified in this supplement." In a communication dated March 12, 2001, Asta Medica provided further clarification about the patent by stating "Asta further confirms that the '172 patent does not cover the drug product as approved in the original Mesnex NDA." Asta also stated that "the '172 patent could have been listed in the Orange Book as of its issuance on December 9, 1997 as covering the 1 gram vial of Mesnex." Thus, with respect to the 1 gram multiple-dose vial of Mesnex, the agency considers the '172 patent to be late-filed under 21 CFR 314.94(a)(12)(vi) and will not require ANDA applicants to certify to this patent.

Conclusion: No safety or effectiveness issues are associated with the proposed approval of American Pharmaceutical Partners ANDA 75-811 for Mesna Injection, 100 mg/mL packaged in 10 mL multiple-dose vials. The recently approved change in specification for the pH range of the reference listed drug product, Mesnex Injection of Asta Medica was made to gain approval of a 3 year expiration date. This has no bearing of the proposed approval of APP's ANDA which will have a 2 year expiration date. In addition, the agency considers the recently submitted '172 patent of Asta Medica to be "late-filed" under 21 CFR 314.94(a)(12)(vi) and will not require ANDA applicants submitting an application for the original Mesna formulation to certify to this patent. All scientific reviews having been successfully concluded, there is no regulatory reason to withhold approval of APP's application for Mesna Injection under ANDA 75-811.

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APPROVAL PACKAGE SUMMARY 75-764

ANDA: 75-764

FIRM: Gensia Sicor Pharmaceuticals, Inc.

DRUG: Mesna

DOSAGE: Liquid Injection

STRENGTH: 100 mg/mL

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 8/24/00

BIO STUDY/BIOEQUIVALENCE STATUS: Bio waiver was granted 3/16/00

METHODS VALIDATION: Methods validation are Pending.

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at 40 ±2°C/ambient humidity, 12 months room temperature 27.5 ± 2.5°/ambient temperature and 3 months stability data at 5±3°. The stability samples stored upright and inverted positions.

LABEING REVIEW STATUS: Labeling is satisfactory 10/10/2000

STERILIZATION: Microbiology portion of the application is satisfactory 3/28/01

BATCH SIZES: The firm has provided the master formula and production procedure for intended production batch ——. The firm has provided a copy of the exhibit batch lot #X99J202 for —— The firm will be using the same drug substance manufacturer, same process and same equipment.

COMMENTS: The application is Approvable Pending method validation.

/S/

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 4/3/01

4/11/01

SUPERVISOR: Paul Schwartz, Ph.D. DATE: 4/6/01

/S/

4/11/01

GensiaSicor™
PHARMACEUTICALS
A sicor... Company

March 29, 2001

N/AC

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

RE: ANDA: 75-764
Mesna Injection, 100 mg/mL

AMENDMENT

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 75-764, for Mesna Injection, 100 mg/mL, which was submitted on December 22, 1999. Reference is also made to the ANDA Method Validation Letter dated March 12, 2001.

Pursuant to the ANDA Method Validation Letter request, we are hereby amending this application to provide updated test methods, in accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21.* Minor revisions to the following methods were made subsequent to the submission of our ANDA 75-764:

The description and justification of the revisions made are found in Section 2.0 of each method listed above.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808. I can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe
Director, Regulatory Affairs

H:\DATA\RG\Mesna\Amends\Amend5.doc

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 30 2001
OGD

cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

000003

GensiaSicor™
PHARMACEUTICALS
A sicor Company

April 6, 2001

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NC

[redacted] CORRESP / ISI

NAI
4/23/01

RE: Mesna Injection, 100 mg/mL
ANDA No. 75-764

PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 75-764, for Mesna Injection, 100 mg/mL, which was submitted on December 22, 1999. Reference is also made to our amendment dated November 3, 2000, which certified that on November 1, 2000, ASTA Medica AG and Bristol-Myers Squibb (plaintiffs), filed a patent infringement lawsuit in the United States District Court, Southern District of New York, against Gensia Sicor and Sicor (defendants). The case was identified in our submission as Civil Action No. 00CIV.8371. Both, ANDA No. 75-764 for Mesna Injection and ANDA No. 75-874 for the Ifosfamide Injection/Mesna Injection Kit were identified in the complaint.

Pursuant to a request by Ms. Elaine Hu, Project Manager, Office of Generic Drugs, we hereby amend this application to provide the current status of the legal action filed against Gensia Sicor and Sicor for patent infringement of U.S. Patent No. 5,696,172. The litigation has commenced and the lawsuit is in the discovery phase of the case. To date, there is no court decision with regard this case.

We trust that the information provided in this amendment is satisfactory for your final review and tentative approval of the ANDA. Should you have any additional questions regarding our amendment, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs
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CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 09 2001
OGD

cc: Mr. Alonza Cruse, District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92612

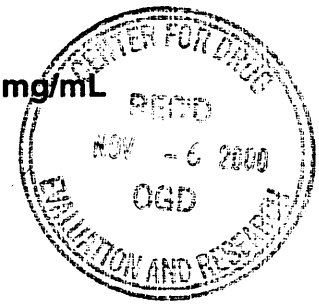
GensiaSicor™
PHARMACEUTICALS
A sicor Company

NAJ 11/8/00
JSI

November 3, 2000

NEW CORRESP
NC

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773



RE: Mesna Injection, 100 mg/mL
ANDA No. 75-764

PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 75-764, for Mesna Injection, 100 mg/mL, which was submitted on December 22, 1999. Reference is also made to our amendment dated September 14, 2000, for a Paragraph IV Patent Certification to **U.S. Patent No. 5,696,172.**

In accordance with the provisions of Section 314.95(e) of the *Code of Federal Regulations*, *Title 21*, we hereby amend this application to document receipt of the notice required under Section 314.95(a) for each person provided the notice. Gensia Sicor has been unable to secure a return receipt from ASTA Medica AG. However, the receipt of notice has been acknowledged in the lawsuit filed by Bristol-Myers Squibb and ASTA Medica AG (see attached). Paragraph 13 of the lawsuit indicates that ASTA Medica AG received notice on September 26, 2000. Based upon this date of receipt, we estimate the 45-day period in which ASTA Medica AG may file a patent infringement lawsuit expires on November 10, 2000.

In accordance with the provisions of Section 314.107(f)(2) of the *Code of Federal Regulations*, *Title 21*, and in regard to **U.S. Patent No. 5,696,172**; we also amend this application to notify the Agency that a legal action for patent infringement has been taken by the NDA and patent holder, ASTA Medica AG. This action was filed within 45 days of receipt of the notice of patent certification. We certify that on November 1, 2000, ASTA Medica AG and Bristol-Myers Squibb (plaintiffs), filed a patent infringement lawsuit in the United States District Court, Southern District of New York, against

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

Gensia Sicor and Sicor (defendants). The case is identified as Civil Action No. 00CIV.8371. ANDA No. 75-764 for Mesna Injection and ANDA No. 75-874 for the Ifosfamide Injection/Mesna Injection Kit were both identified in the complaint. A copy of the complaint for patent infringement is attached.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-4724 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Director, Regulatory Affairs

H:\DATA\IRG\Mesna\Amends\Patent Amend4.doc

Attachment
cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92612

GensiaSicor™
PHARMACEUTICALS
A silicon... Company

September 18, 2000

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N/Ac

RE: ANDA: 75-764
Mesna Injection, 100 mg/mL

MAJOR AMENDMENT
CHEMISTRY, MICROBIOLOGY AND LABELING

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application, ANDA 75-764, for Mesna Injection, 100 mg/mL, which was submitted on December 22, 1999. Reference is also made to the Agency's facsimile dated July 10, 2000.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21,* we are hereby amending this application to provide the additional **chemistry, microbiology and labeling** information requested.

In addition, we are also amending this application to provide revised documents to change the pH range (i.e., 6.5 to 7.4). The revision in pH range was precipitated by the recent patent, U.S. Patent No. 5,696,172, granted to the innovator, Asta Pharma AG, for Mesnex® (Mesna Injection). The documents (i.e., **Compounding Production Record**, **In-Process Production Record**, and **Stability Protocols**) reflecting the pH revision are provided in **Attachment 12**.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting me at (949) 457-2808. I can also be contacted by facsimile at (949) 583-7351.

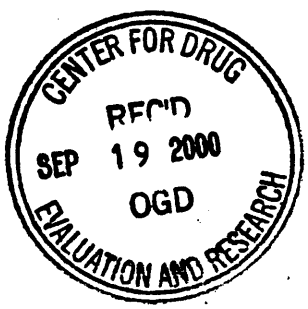
Sincerely,

Rosalie A Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\RG\Mesna\Amends\Amend3.doc

cc: Acting District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715



ANDA 75-764

Gensia Sicor Pharmaceuticals, Inc. FEB 15 2000
Attention: Rosalie A. Lowe
19 Hughes
Irvine, CA 92618-1902

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Mesna Injection, 100 mg/mL

DATE OF APPLICATION: December 22, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 23, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research