

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
20-855**

**Medical Review(s)**



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

**MEDICAL OFFICER REVIEW**

**NDA NUMBER:** 20-855

**DRUG NAME:** Mesna

**INDICATION:** Mesnex has been shown to be effective as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis

**SPONSOR:** Asta Medica

**CLINICAL REVIEWER:** Gerald H. Sokol MD, MS, FCP

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# **The Executive Summary of the Primary Clinical Review**

## **1. Recommendations**

### **1.1 Recommendation on Approvability**

From a clinical standpoint the NDA is approvable. Neither submitted major pivotal study demonstrated statistical significance, however, there were equal incidences of hematuria (the primary efficacy parameter) in both arms of both submitted studies-0018 and 3126.

In the resubmitted Study-0018 (previously rejected secondary to issues of scientific integrity) two incidences of hematuria occurred-one in each study arm. In Study 3126 (designed predominantly as a PK equivalency trial between iv/iv/iv and iv/po/po, with observation of adverse events and incidence of hematuria), there was one occurrence of grade 3 or 4 hematuria in each study arm. As Study 3126 was not designed to show efficacy and was not powered to show equivalence between the two mesna regimens, no statistical test was performed for that trial (but for the PK aspects).

Study 3126 demonstrated that the plasma AUC for the iv/po/po regimen resulted in higher exposure (129-151%) compared to the already approved iv/iv/iv mesna regimen. Likewise, the urinary levels of mesna for the iv/po/po regimen were higher than for the iv/iv/iv regimen suggesting the likelihood of at least, comparable uroprotection against ifosfamide. Ifosfamide concentrations were not significantly affected.

The incidence of nausea was higher in the iv/po/po mesna arm. Biopharmaceutic review and analysis did indeed suggest a relationship between mesna exposure (AUC) and the first occurrence of nausea (p value .026 for AUC). The convenience of po mesna must be weighed against the possibility of its greater induction of nausea.(small number of patients)

There was a concern regarding the higher incidence of acidosis reported in the po mesna arm. Fanconi-like renal tubular acidosis has been well described as an adverse effect associated with ifosfamide. Review of all clinical data in study 3126 indicates that 2 patients receiving po mesna and reported to have sustained acidosis were not acceptable candidates for po mesna because of esophageal obstruction difficulties. Acidosis seemed to be equally prevalent in the two arms after review of the case report forms.

An additional recurring concern regarding both iv and po mesna is the possibility of tumor protection by mesna as well as a potential interference by mesna with the

active species of ifosfamide. In both the 1988 and 1997 submissions data was presented with respect to this question. Preclinical pharmacological data, patient response data in the controlled trials and hematological toxicity (a surrogate for anti-tumor activity) all indicated no evidence of tumor protection. In addition non-controlled studies utilizing high doses of ifosfamide (3-5gm/m<sup>2</sup>) in combination with IV mesna in ratios of 1:1 demonstrate clinically acceptable response rates, though do not specifically address the possibility of some degree of tumor protection.

## **1.2 Recommendation on Postmarketing and/or Risk Management Steps**

It is not clear whether the oral dose of mesna is optimal as PK analysis suggests greater than IV plasma and urinary levels of mesna and no greater protection against ifosfamide induced urotoxicity than the IV mesna. On the other hand the greater AUC of po mesna as administered in Study 3126 provides an element of reassurance regarding potential lack of oral bioavailability. It should be noted that the optimal dose of IV mesna for higher-dose ifosfamide regimens is not known.

No additional data exists regarding, age, ethnic or special population influences on mesna PK. A gender effect analysis was conducted in four male and four female volunteers; no differences in plasma pharmacokinetics were detected.

Lastly ifosfamide is known to be associated with acidosis (renal tubular-like acidosis). The detection and management of this adverse effect should be defined in for both mesna and ifosfamide.as they are utilized together.

## **2. Summary of Clinical Findings**

### **2.1 Brief Overview of Clinical Program**

Product name-Generic-Mesna, Trade-Mesnex, Chemical-Sodium-2-mercaptoethane sulfate

Class-Uroprotector

Route of administration-iv followed by tablets-400 mg .The proposed dose is an iv dose of mesna at 20% of the ifosfamide dose at time 0, followed by po doses of mesna at 40% of the ifosfamide dose administered at times 2 hours and 7 hours after ifosfamide dosing.

Indication and population studied-" Mesnex has been shown to be effective as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis".

Population studied-a total of 17 patients with a diagnosis of metastatic sarcoma was studied in Study 3126 to address PK equivalency and adverse drug effects.

**The number of primary safety and efficacy trials**-New clinical data from one PK trial, was submitted. Safety and adverse event observations were included in the study. A reanalysis of a previous safety and efficacy trial (0018) was submitted. Data submitted from the March 15, 1997 submission was referenced including controlled trial MD-504.

**Number of patients enrolled in the primary trials**-17 patients were enrolled in this NDA amendment. Review of the previously submitted (March 15, 1997) NDA was briefly conducted. That submission contained 3 controlled trials: 0018, MED504, 0019(123 patients) and 3 uncontrolled trials: D-0016, MED700, MED200 (230 patients)

**Overall number of patients in the safety data base**-the safety data base was comprised by the patients cited above and other Phase I and II trials previously submitted.(See Section 4)

## **2.2 Efficacy**

Though one of the two pivotal trials previously submitted ( 0018) did not attain statistical significance, the weight of clinical and PK data support the indication cited. No specific population for use has been identified.

The major trial submitted (3126), was conducted to compare the PK of mesna, dimesna and ifosfamide in urine and plasma after an iv vs an iv/oral regimen in patients treated with ifosfamide. It was an open, multicenter, randomized, multiple dose, 2-way crossover study. The secondary objectives of the study included the PK evaluation of ifosfamide in blood as well as safety (including hematuria as a safety rather than an efficacy measure). The rationale of the study was to supplement study 0018 that was deemed insufficient in its previously submitted form.

Study 0018 was an open label, randomized, comparative, 2-way crossover, multiple dose study of efficacy and safety of an iv vs iv/oral regimen of mesna in patients treated with ifosfamide. The objectives of this study were to compare the clinical efficacy of the two regimens in the prevention of severe hematuria, to compare safety and tolerability of the two regimens and to provide some PK data for mesna in plasma and urine. Sixty-six patients were enrolled.

In summary, oral mesna following an initial dose of iv mesna provides comparable uroprotection to an all iv regimen. Studies 3126 and 0018 show a comparable incidence of hematuria in ifosfamide treated patients, (in both studies, only one incidence of grade III or IV hematuria occurred in each arm). Statistical significance was reached in the second cycle, but not in the first. This is considered to be related to small sample size, which increases due to the crossover design in the second cycle.

From the PK standpoint, the plasma AUC for an iv/po/po regimen achieved higher levels of mesna (129-151%) compared to the alternative Agency approved iv/iv/iv schedule. For the iv/po/po regimen, urinary levels of mesna on day 5 were higher than those on day 1, while that was not the case for the iv only schedule. PK profiles of ifosfamide were determined to be similar in the two regimens. Exploratory PK/PD analysis indicated that the exposures (AUC) of mesna were related to time of first occurrence of nausea, likely explaining the higher incidence of nausea in the iv/po/po arm.

Study 0018, study 3126 and other randomized data from 504 provided in the previous NDA supports approval for the indication requested. Data from the previously submitted NDA also provides a plethora of non-controlled data supporting the efficacy of mesna in mitigating urotoxicity of ifosfamide. Study 0018, study 3126 and the data provided in the previous NDA support approval for the indication requested.

In spite of an increase in nausea and perhaps vomiting, the flexibility of an outpatient oral regimen appears to be a patient advantage. Though bladder irrigation and n-acetylcysteine have been used, no other acceptable prophylactic agent or treatment exists to mitigate ifosfamide induced urotoxicity.

The appropriate dose of oral mesna for doses of ifosfamide other than 2.0g/m<sup>2</sup> for five days remains undefined.

### 2.3 Safety

A review of Phase I and II trials supporting the safety profile of oral mesna was provided in the previous NDA submission. This review deals primarily with Study 3126 and to a lesser extent Study 0018.

Study 0018, as originally reviewed did demonstrate a higher incidence of death (4 deaths) on the iv/po/po vs. 1 death on the iv only first cycle. This remains unexplained. No greater incidence of death has been seen in the iv/po/po regimen in study 504. There were no deaths in Study 3126.

In study 0018 there were no trends indicting clinically significant differences between the two arms with respect to albumin, BUN, cholesterol, electrolytes, liver function tests, urinalysis, platelets or blood counts. No significant variation in laboratory parameters between the two study arms were noted in 3126.

Treatment Emergent Signs and Symptoms reported in Study 3126 were nausea, fatigue, constipation, vomiting, hematuria, anemia, insomnia, pallor, alopecia, tachycardia, edema, acidosis, back pain, diarrhea, granulocytopenia, and somnolence. Allergic reactions and neuropathy have also been reported. Study 0018 reflects similar adverse effects. Separating the side effects of mesna from

those of ifosfamide is extremely difficult as the agents are used together and ifosfamide induces all of the adverse effects of an alkylating cytotoxic agent.

The sponsor reported a higher incidence of acidosis in the iv/po/po sequence in study 3126. Review of the case report forms however, indicated an equal and significant incidence of acidosis in both groups of patients (8/16). Two of the iv/po/po patients who had acidosis had esophageal obstruction or stasis and were not suitable candidates for the study of a po medication. Details related to acidosis were not collected prospectively (including arterial pH) and therefore a full discussion is not possible.

#### **2.4 Dosing, Regimen and Administration**

The proposed dose and schedule of mesna is supported by the data in the NDA and the current amendment. It is not clear if lower doses of mesna might be just as efficacious and avoid its enhancement of nausea. Likewise it is not clear that the ratio of iv and oral mesna would be appropriate for all doses of ifosfamide. Future studies must address those concerns.

Biopharmaceutics review of study 3126 suggests the association of higher mesna AUC levels with the earlier onset of nausea. The convenience of an oral mesna regimen must be weighed against the side effect of enhanced nausea in the po regimen.

#### **2.5 Drug-drug Interactions**

No data on drug-drug interactions has been provided. Available data suggests no impairment of cytotoxic efficacy.

#### **2.6 Special Population**

Of the 17 patients submitted in study 3126, there were 7 males and 10 females, 1 Black patient and 16 Whites. The mean age of subjects in the IV +PO/IV arm was 39.3 (range 25-57) and the mean age of the IV/IV+PO subjects was 47.4 (range 19-74). Therefore data is insufficient to draw conclusions with respect to special populations regarding safety or efficacy.

A previous study submitted in 1997 was conducted in four male and four female volunteers. A gender effect analysis demonstrated no differences in plasma pharmacokinetics.

# 1. Clinical Review

## 1.1 Introduction and Background

### 1.1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups

Reference is made to the Medical Officer Review of mesna tablets dated March 25, 1998.

1. Name of drug - Generic-Mesna, Trade-Mesnex, Chemical-Sodium-2-mercaptoethane sulfate.
2. Proposed indication-"Mesnex \_\_\_\_\_ as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis".
3. Dosage form-400 mg tablets for oral administration. The proposed regime is an initial iv dose of mesna at 20% of the ifosfamide dose at time 0, followed by po doses of mesna at 40% of the ifosfamide dose administered at times 2 hours and 4 hours after ifosfamide dosing.
4. Related drug- IV mesna.
5. NDA submission dates-March 25, 1997. Official submission date-September 18, 2001.
6. Age Groups- not specified.

## 1.2 State of Art for Indication

No other agent has been Agency approved for the indication cited. N-Acetyl cysteine, hydration and bladder irrigation have been utilized in uncontrolled studies.

## 1.3 Important Milestones in Product Development and Other Relevant Information

Mesna for IV injection was approved for the prevention of ifosfamide (I)- induced hemorrhagic cystitis under NDA 19-884 in 1988. To prevent the necessity for prolonged hospitalization, an oral formulation was developed. Ultimately a 400 mg film-coated tablet was developed, \_\_\_\_\_ providing a stable formulation resistant to change in dissolution rate on storage and devoid of adverse taste consequences. Oral administration of a mesna solution or oral intake of the IV Mesnex has been approved by drug regulatory agencies in Canada, Great Britain, and Germany. Mesnex tablets have been approved in Germany, Great Britain, the Netherlands, Italy, and Denmark for the prevention of ifosfamide-induced hemorrhagic cystitis.

NDA-20-855 for Mesna-400 mg tablets was submitted on March 20, 1997. Agency review was completed on March 25, 1998, with the finding that the information submitted was inadequate for Agency approval secondary to the deficiencies cited below:

“ Serious deficiencies in monitoring of the controlled US study ( D-07093-0018) have been identified by FDA’s DSI. These new findings call into question the validity of the study results, which provided the critical urinary PK data upon which bioequivalence was based and also provided important safety information”.  
“ The findings from the controlled US study (D-07093-0018) did not achieve statistical significance when the data were re-analyzed using only the first cycle data and excluding 12 patients from center 5 (Rosenthal) and 5 patients who discontinued from study prematurely.

There were other comments and requests for information relating to PK and chemistry which were to be addressed but were not the issues preventing approval.

On March 8, 2001 an NDA Resubmission meeting was conducted to discuss the proposed content and format of the amendment to the Mesnex tablet NDA and to discuss biopharmaceutical issues related to related to Study D-0709-3126. That meeting resulting in the conduct of the study defined below.

The Agency concurred with the sponsor that an amendment as specified below would be a sufficient response to the March 25, 1998 Deficiency Letter.

“.... We propose to submit in the amendment a report of the PK Study of IV vs. IV plus oral mesna in patients treated with Ifex (D-07093-3126), along with a report of the reanalysis of the efficacy in study D-07093-0018 (excluding the Rosenthal data), a report on the human serum protein binding of Mesnex Tablets, along with revised integrated summaries. In addition, the amendment will include the response to the CMC deficiencies noted in the “Not Approvable” Letter, as well as financial disclosure certifications for the two clinical trials and a Pediatric Use Statement...”

#### **1.4 Important Issues with Pharmacologically Related Agents**

No other similar pharmacological agents have been evaluated.

## **2. Clinically Relevant Findings From Chemistry, Animal Pharmacology/ Toxicology, and Microbiology**

There appear to be no Chemistry or Microbiology issues remaining. Animal pharmacology has been reviewed extensively in the original NDA submission. No animal pharmacology has been submitted with this supplement.

### 3. Human Pharmacokinetics and Pharmacodynamics

The Sponsor's focus in Study 3126 is to compare the PK after 5 days of consecutive dosing of mesna and dimesna in plasma and urine and of ifosfamide in plasma from an iv/iv/iv vs. an iv/oral/oral administration of mesna. In addition, data on safety and tolerability of the two regimens will be collected. This study (Study No. D-07093-3126) was submitted to supplement data in the previously submitted non-approvable NDA. Only the submitted PK/PD study 3126 will be reviewed in depth in this submission but a brief review of mesna's pharmacokinetic and pharmacodynamic properties follows.

#### **Brief PK/PD review**

Mesna was developed as a prophylactic agent to prevent the hemorrhagic cystitis induced by ifosfamide. Similar to the cysteine-cystine system, following IV injection, 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 mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxyifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxyifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and other urotoxic metabolites. (Labeling information).

Mesna is Agency approved for the above indication. After administration of 800 mg of mesna the half-lives of mesna and dimesna in the blood are .36 and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose is 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

Ifosfamide has been shown to have dose-dependent pharmacokinetics in man. 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 metabolites of ifosfamide, repeated doses of mesna are required. Based on the above data during IV administration of ifosfamide, mesna is given by bolus doses prior to ifosfamide and 4 and 8 hours after ifosfamide administration at doses equal to 20% of the ifosfamide dose (the total daily dose of iv mesna is 60% of the ifosfamide dose).

### 4. Description of Clinical Data and Sources

#### 4.1 Sources of clinical Data

##### **Submitted Data**

The Sponsor has submitted in 29 volumes the following information:

- Revised Proposed Package Insert
- Revised CMS data and response to the FDA Action Letter
- Human PK bioavailability, and clinical data (mesna tablets), in vitro studies (human protein binding, — assay validation studies, Ifosfamide (I) validation assay and a new in vivo final clinical study report pertaining to study D-07093-3126 (PK of mesna, dimesna and I after an IV and IV/oral regimen of mesna in patients treated with I)
- Clinical/Statistical data including a Pediatric Waiver Request, revised summaries of safety and efficacy, a new final study report of D-07093-3126, revised clinical study report D-07093-0018 (Open Label, Randomized, Comparative, Multiple-dose, Two-way Crossover Study of the Efficacy and Safety of an IV and IV/PO Regimen in patients treated with Ifosfamide) as well as geriatric information and literature references.
- Case report forms and tabulations.

## 4.2 Overview of clinical data

### 4.2.1. D-07093-3126

“The study is an open label, randomized, multiple dose, two-way crossover study with 12 patients in both mesna dosing regimens. The objective was to compare, after 5 days of consecutive daily dosing, the PK of mesna and dimesna in plasma (day 5) and urine (days 1 and 5), and of I in plasma (day 5) following and IV/IV/IV vs. IV/oral/oral administration of mesna. Safety and tolerability were observed. This study will be the pivotal study for review.

Study Centers-University of Michigan, Dana Farber Cancer Center, and Columbia University.

### 4.2.2. Re-analyzed study D-07093-0018

Study D-07093-0018 was an open label, randomized, comparative multiple-dose two way crossover study of the efficacy and safety of an IV and IV/PO regimen of mesna in patients treated with ifosfamide. The objectives of this study were to recruit 120 patients (study was closed early-71 recruited, 71 eligible for safety, 58 for ITT analysis and 40 for PP analysis): 1) to compare the clinical efficacy of two regimens, mesna IV and IV + PO, in the prevention of I-induced severe hematuria (>50 RBC's/hpf or visible blood); 2) to compare the safety and tolerability of the two regimens 3) to collect comparative PK data for mesna and dimesna at selected centers. The criteria for efficacy and safety were the rates of

severe micro and macro hematuria and adverse events. This study was thoroughly reviewed in the previous submission and will not be reviewed again in depth.

#### **4.3 Postmarketing Experience**

Mesna for IV injection was approved for the prevention of ifosfamide-induced hemorrhagic cystitis under NDA-19-884 in 1988. To prevent the necessity for prolonged hospitalization an oral formulation was developed. Ultimately a 400 mg film-coated tablet was developed ( [REDACTED] ) providing a stable formulation resistant to change in dissolution rate on storage and devoid of adverse taste consequences. Oral administration of a mesna solution or oral intake of Mesnex has been approved by drug regulatory agencies in Canada, Great Britain, and Germany. Mesnex tablets have been approved in Germany, Great Britain, the Netherlands, Italy, and Denmark for the prevention of ifosfamide-induced hemorrhagic cystitis. Adverse drug reports to the Agency regarding IV mesna are usually combined with those relating to ifosfamide as the two agents are utilized together.

#### **4.4 Literature Review**

There is a plethora of published literature relating to mesna in both its iv and po forms. Table II summarizes the major literature contributions pertaining to oral mesna

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**Table 1: Literature References**

Journal	Author	Drugs Used (Dose)	Mesna Formulation	# Urotoxicity
Cancer Chemo	Andersen	I 1.5g/m <sup>2</sup> x8, VP16	iv, po low dose (200 po)	3/47
Euro J Cancer	Araujo	I 2250 mg/m <sup>2</sup> x4 + ?	840 mg po q4 x3	10/70 microhem
J Surg Onc	Araujo	I 3 gm/m <sup>2</sup> x5 + Cisplatin	40% of I dose	2/21 microhem
Brit J Ca	Bleehan	VP16, I 5 gm/m <sup>2</sup> x1	po or iv	3/149 cystitis
19 <sup>th</sup> Cong Abst	Bordenave	I 2 g/m <sup>2</sup> x1, Cisplatin	po 1000 mg/m <sup>2</sup> x2	no urotoxicity
Oncology	Brocato	I 2.5 g/m <sup>2</sup> x2, Epirubicin, Cisplatin	40% of I dose	gr1:56/1046, gr2: 24/1046
Sem Onc	Cabanillas	I 1.33 g/m <sup>2</sup> x3, VP16	500 mg (sol)	no macrohem
Brit J Ca	Cerny	I 2 g/m <sup>2</sup> x3, po VP16	400 mg at 0, 4, 8 hr	no urotoxicity
J Ca Res Cl Onc	Cerny	I 1.75g/m <sup>2</sup> x5 infusion	400 mg po at 4, 8 hr	no urotoxicity
Ca Chemo Pharm	Cervellino	I 3.5 g/m <sup>2</sup> x5 infusion	40% of I dose at 10, 12 hr	3/18 microhem
Oncology	Cervellino	I 3.5 g/m <sup>2</sup> x5 infusion	40% of I dose at 10, 12 hr	3/28 microhem
ASCO	Cervellino	I 3 g/m <sup>2</sup> x3, Epirubicin	40% of I dose	Urotoxicity < 2%
Acta Onc	Cervellino	Cisplatin, I 2.5 g/m <sup>2</sup> x5	1000 mg/m <sup>2</sup> po x1	1/30 gr3 urotoxicity
ASCO	Rohrbach-Klinik	I po?	po?	0/127 hematuria
JNCI	Edmonson	I 2.5 g/m <sup>2</sup> x3, VP16	iv and po?	1/44 gross hematuria
Sem Onc.	Elisson	I 1.4 g/m <sup>2</sup> x3, Dox, VCR, VP16	iv, po 1000 mg	18/36 micro; 1/36 macro
Ann Onc	Frustaci	I 1.8 x5, 2-2.5 x2, 3 g/m <sup>2</sup> x2	po (80%)	0/27 UTI symptoms
Amer J Clin Onc	Gonzalez	Mito, I 5 g/m <sup>2</sup> x1, Cisplatin/Vin I/Cisplatin	1600 mg/m <sup>2</sup> po at 4, 8, 12 hr	15% gr1-2; 7.1% gr1-2
ASCO	Goodman	I 1-1.5 g/m <sup>2</sup> x3	iv and po	0/6 hem cystitis
ASCO	Goodman	I	iv and po (40%)	1/60 gross hematuria
Sem Onc	Goren	I - various doses	iv and po (2 doses)	review of 47 studies and of 6475 courses
Br J Can	Highley	po I 0.5 g bid x14d	po 60% of I dose bid	1/42 hematuria
Amer J Cl Onc	Holoye	I 2 g/m <sup>2</sup> x5	po 400 mg at 4, 8 hr	20: 6-10 RBC;

Journal	Author	Drugs Used (Dose)	Mesna Formulation	# Urotoxicity
				3:11-50 RBC
J Can Res Clin Oncol	Katz	I various doses	po at 8 hr, 2x I dose	1.4% microhem
ASCO	Lemke	I 1 g/m <sup>2</sup> x3, Cisplatin	iv and po 400 mg/m <sup>2</sup> at 2, 6 hr	0/15 hem cystitis
J Clin Onc	Leone	I 2 g/m <sup>2</sup> x3, Vinorelbine	iv and po 800 mg/m <sup>2</sup>	6/45 gr1-2 cystitis
J Clin Onc	Murad	Bleo, I 2 g/m <sup>2</sup> x3, Carbo	iv and po 40% of I dose at 8 hr	3/35 gr2; 6 gr1 hematuria
Tumori	Nobile	I 1.8 g/m <sup>2</sup> x5	iv 360 or po 720 mg/m <sup>2</sup>	po: 8/57 courses hematuria; iv: 6/72
J Clin Onc	Perez	I 2 g/m <sup>2</sup> x3, Mitoxantrone	po 2000 mg at 8 hr	2/48 gr2; 4/48 gr1
ASCO	Rabinovich	I 2 g/m <sup>2</sup> x3, Cisplatin	800 mg/m <sup>2</sup> at 8 hr	1/23 gr1 hematuria
J Clin Onc	Rodriquez	MINE, ESHA I 4 g/m <sup>2</sup> over 4d	500 mg po, 4g iv	0 episodes hematuria
Can Chem Pharm	Thatcher	I 5 g/m <sup>2</sup> x1	iv 5 g/m <sup>2</sup> + po 3 gm/m <sup>2</sup> x3 at 4, 8, 12 hours	4% mild cystitis
Can Chem Pharm	Toma	Epirubicin, I 1.5 g/m <sup>2</sup> x5	40% of I dose, solely po	0/16 hematuria
Cancer Invest	Turill	Carbo, I 1.5 g/m <sup>2</sup> x4	400 mg/m <sup>2</sup> qid po	8/25 microhematuria
Amer J Clin Onc	Vallejo	I 2 g/m <sup>2</sup> x3, Vinorelbine	iv + 2000 mg po at 8 hr	2 gr1; 1 gr2 hematuria
12 Int Conf Chem	Varini	I 1.2 g/m <sup>2</sup>	none vs 500 mg/m <sup>2</sup> at 4, 8 hr	44% vs 17% microhem wo/w mesna
	Varini	I 1.8 g/m <sup>2</sup> x5	iv 360, then 720mg/m <sup>2</sup> po x2 vs 720 mg/m <sup>2</sup> po at 0, 4, 8 hr	iv/po: 17% microhem po: 18% macro + 18% micro
Amer Soc Clin Onc	Vincent	I 250mg po	po 200 mg bid	5% mild to mod hematuria

I = Ifosfamide

## **5. Clinical Review Methods**

### **5.1 How Review was Conducted**

NDA submissions of 1988 for IV mesna and 1998 for NDA mesna tablets along with Biopharmaceutical and Statistical reviews were reviewed for pertinent information. Trial D-07093-0018 was reviewed as previously submitted and as currently reappraised by the sponsor. Major review was allocated to the pivotal new study D-07093-3126. Literature was reviewed but added little except as noted under 7.0.

### **5.2 Overview of Materials Consulted in Review.(See Section 1.1 and 5.1).**

An electronic data base was submitted and was utilized along with 29 volumes.

### **5.3 Overview of Methods Used to Evaluate Data Quality and Integrity.**

DSI clinical inspection of the University of Michigan study site was conducted on March 5, 2002. At the study site there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, and were available for the duration of the study. All enrolled subjects received the assigned study medications, had clinical and laboratory parameters recorded, completed the study, and had their primary efficacy endpoint captured. Instances of deviations from the protocol, inaccurate record keeping, and inadequate concomitant medication reporting were found, which were not of clinical significance to require exclusion of any subject except #37 from data analysis. The exclusion of patient #37 does not materially change the results of the study. An amended DSI report is anticipated.

Medical officer review appraised consistency between central laboratory data and study center data. Lack of or missing data on study reports was reviewed. Every patient clinical chart as presented in the case report form was individually reviewed, particularly for safety as pertaining to nausea and vomiting and acidosis. Compliance with inclusion criteria and other study criteria including endpoint analysis was reviewed.

### **5.4 Were the Trials conducted in Accordance with Accepted Ethical Standards**

Trials were conducted within acceptable ethical standards.

### **5.5 Evaluation of Financial Disclosure**

The sponsor provided financial disclosures. There were no financial disclosures submitted that could cast doubt on the findings.

## 6. Integrated Review of Efficacy

### 6.1 Brief Statement of Conclusions

#### 6.1.1. Study 3126-Pharmacokinetics of Mesna, dimesna, and Ifosfamide after an iv and iv/po Regimen in patients Treated with Ifosfamide

Study-3126 was a Phase II PK multicenter, open label, randomized, multiple dose crossover study. Patients with metastatic sarcomas were to receive a fixed (later amended to varying doses of ifosfamide) dose of 2 gm/m<sup>2</sup> of ifosfamide. Patients were randomly assigned to either a iv/iv/iv schedule or an iv/oral /oral regimen of mesna with the oral doses prescribed as 400 mg tablets (the study medication), followed in the second cycle by the alternative dosing schedule. The mesna iv doses consisted of administration of mesna at a fixed 20% dose of the ifosfamide dose given at time 0, 4 hours and 8 hours, while the two po mesna doses in the iv/po/po arm consisted of 40% of the ifosfamide dose and was given at 2 hours after the initiation of ifosfamide and the iv dose of mesna and at 6 hours.

The first objective of the study was to investigate the PK of mesna and its metabolite, dimesna, in blood and urine following the administration of iv or iv/oral mesna in ifosfamide treated patients. The secondary objectives of the study included the evaluation of the PK of ifosfamide in the blood and evaluation of the safety (adverse drug events, the incidence of severe hematuria), and tolerability of the mesna treatment schedules. In addition, the rationale of study 3126 was that it would supplement the previously submitted study 0018 which was deemed insufficient in the previous NDA submission.

In the Agency biopharmaceutics analysis, Study 3126 demonstrated that the plasma AUC for iv/oral/oral regimen achieved, if anything, an overcompensation of 129-151% compared to the alternative Agency approved iv/iv/iv schedule. In this study, during the five days of ifosfamide dosing, the trough levels of mesna, dimesna and ifosfamide were measured. Only rarely was the trough level of mesna or dimesna in the iv/iv/iv regimen detectable while it was detectable most of the time in the iv/po/po regimen. Similarly, urinary mesna excretion on days 1 and 5 indicated that the urinary levels of mesna on day 5 were higher than on day 1 for the iv/po/po schedule, compared to the iv/iv/iv schedule.

Urinary levels of mesna for the iv/po/po regimen showed that urinary levels of mesna on day 5 were higher than that on day 1 while that was not the case for the iv/iv/iv schedule. In addition, the urinary levels for mesna for the iv/po/po schedule are higher than that for the iv/iv/iv regimen (particularly on day 5) suggesting an accumulation of mesna in plasma.

It was not clear that an elevated or prolonged exposure to mesna would effect ifosfamide PK. Review of the data showed that the PK profiles of ifosfamide were determined to be similar in the two regimens.

Lastly, Agency Biopharmaceutics PK/PD analysis demonstrated that exposures (AUC) were related to time to first occurrence of nausea (p value 0.026 for AUC) possibly explaining the higher incidence of nausea in the iv/po/po arm.

The Sponsor concluded that the iv/po/po regimen resulted in plasma peak concentrations at the same times as the conventional iv/iv/iv regimen, because the times of oral dosing accounted for a delayed tmax compared to iv dosing

The two oral mesna doses of the iv/po/po schedule were increased over the corresponding iv doses of the iv/iv/iv regimen to compensate for a decrease in bioavailability compared to iv administration. In point of fact, there is an overcompensation that may be associated with a greater incidence of nausea and vomiting. The plasma peak concentrations were lower but longer lasting.

Accumulation of mesna in the plasma was either negligible or absent. This deviates from the Agency Biopharmaceutics review. The maximum mesna excretion rates attained in the urine were similar for both regimens. The minimum rates observed at the end of the 24 hour cycle with the iv/po/po regimen were above the rates observed with the iv/iv/iv schedule.

No accumulation of mesna in the urine was seen after 5 days on the iv/iv/iv regimen; however, after the iv/po/po schedule, due to the sustained renal excretion, an accumulation of the urinary concentrations was observable.

The PK of dimesna in the plasma was similar for both schedules. The sponsor felt that the increased plasma AUC of the iv/po regimen derived from the higher po doses of mesna than in the iv only regimen. Some accumulation of urinary dimesna was seen in the iv/oral regimen.

The plasma PK of ifosfamide were nearly identical in both mesna regimens demonstrating that oral administration of mesna did not have an impact on ifosfamide PK.

The difference between the Agency evaluation and the Sponsor's evaluation was not significant from the PK standpoint. The issue of efficacy is essentially established by data submitted in the previous submission in addition to study 3126. The resubmitted and reanalyzed study 0018 will only briefly be reviewed.

**6.1.2. Study 0018-Open Label, Randomized, Comparative, Multiple-Dose, Two Way Crossover Study of the Efficacy and Safety of an iv and iv/po Regimen of Mesna in Patients Treated with Ifosfamide.**

The objectives of this study were to compare the clinical efficacy of the two mesna regimens, iv only and iv/po, in the prevention of ifosfamide-induced severe hematuria (>50 RBCs/hpf or visible blood), to compare the safety and tolerability of the two regimens, to compare PK data for mesna and dimesna in urine at selected centers. Endpoints consisted of the rate of severe micro-and macro hematuria and adverse events. The two arms of the study and the doses of ifosfamide were similar to those used in study 3126.

As previously submitted, this study was felt to be supportive but failed to reach statistical significance. The number of dropouts in this study was larger than the number of patients sustaining severe hematuria. In the sponsor's analysis there was only one episode of grade III or IV hematuria. This occurred in the iv/po arm but the subject had a history of bladder cancer and had hematuria upon entry into the study. There were no instances of grade III or IV hematuria in the iv only arm. The analysis of the second cycle (felt to be unreliable from the statistical standpoint secondary to the large number of dropouts) indicated one incidence of grade III or IV hematuria on the iv/po arm and one incidence (the same ineligible patient as above) with grade III or IV hematuria in the iv only arm.

The Agency evaluation for the intent to treat (ITT) population indicated an upper confidence bound of 12%, which was higher than the pre-specified equivalence margin of 10% and the upper confidence bound from the per protocol (PP) population was 5.8%. The Agency did not agree with the sponsor's statistical methodology in that two-sided confidence intervals should have been used instead of one-sided intervals and dropouts were handled incorrectly as successes.

The sponsor concluded that equivalent uroprotective efficacy was demonstrated, that the urinary PK portion of the study indicated that the profile of mesna excretion provided a PK rationale for the proposed iv/po regimen, that the 24 hour cumulative urinary mesna excretion did not differ among patients between day 1 and 5 (as opposed to higher dimesna excretion on day 5 than day 1), that there was significant patient variability for both iv only and iv/po arms, and that the safety profile for both mesna regimens suggested that the two formulation schedules were comparable and generally well tolerated.

This study was considered supportive but statistically and methodologically inadequate.

**6.2 General Approach to Review of the Efficacy of the Drug**

A brief review of the studies submitted in the previous March 20, 1997 submission will be provided. The major efficacy review will concentrate on study 3126 as presented in 6.3. Biopharmaceutics and Statistical reviews will be included in the Review of Efficacy.

#### **6.2.1. Previous Studies NDA 20-855 Review-March 20, 1997 submission**

Clinical studies submitted (PK and comparative iv/po studies)

##### **6.2.1.1. D-07093-0007(7)-Drinking Ampoules vs. Film-coated Tablets in Healthy Volunteers.**

This was a crossover study conducted to compare the total urinary excretion rates of free thiols and reduced disulfides between mesna drinking ampoules and mesna \_\_\_\_\_ tablets. Volunteers were randomized to groups that received either 2 gm of mesna as drinking ampoules or 1.5 gm (five 300 mg tablets) of mesna. After a one-week washout period the alternative treatment was given. Urine samples were collected before and periodically after administration.

Mesna was well tolerated. Adverse effects included flu-like symptoms. One subject experienced a sleeping disorder. The mean 24 hour urinary excretion values (% of mesna dose) of free thiols and reduced disulfides after administration of mesna drinking ampoules and of mesna film-coated tablets were essentially equivalent.

##### **6.2.1.2. D-07093-0008-Single Dose Safety, Tolerance and PK Study**

This was a single-center, open randomized, Latin square cross-over design Phase 1 study to evaluate safety, tolerance and PK (plasma and urine) of oral and iv administered mesna. The iv injection solution and single ascending oral doses of 300 mg of \_\_\_\_\_ tablets were given to normal healthy volunteers. Single oral doses of 600-2400 mg as well as single iv doses of 600 mg of mesna were given to each of 10 volunteers with a washout period between dosing. Blood and urine samples were collected at appropriate intervals to determine mesna and dimesna levels. Headache was the most frequent adverse event followed by nausea and vomiting as well as general aches and flushing. The tablets were well absorbed. The absorption and excretion of oral tablets was rapid with a plasma t<sub>max</sub> of less than 3 hours post dosing and detectable urine excretion occurring within the first hour. The mean total plasma bioavailability of the 600 mg

oral dose was 77% for free mesna and 95% of dimesna. For po mesna the AUC values of the 600-2400 doses increased in a linear fashion.

With respect to urinary PK in the 24 hours post-dosing, over 18% of the total oral dose and 37% of the iv dose was excreted in the urine as mesna. Most of the urinary mesna excretion occurred in the first 4 hours. The bioavailability of free mesna in the urine after the 600 mg oral dose was 67.3% of that of the 600 mg iv dose over the 24 hour period and 48.2% for the first 4 hours. The doses of 600-2400 mg demonstrated close dose linearity for the total excretion of mesna and dimesna with the ratio of total mesna and dimesna of 1:1.9:3.8.

#### **6.2.1.3. D-07093-0010-Multiple Dose Safety, Tolerance and PK Study**

This was a randomized four way crossover Phase 1 study in 16 evaluable healthy male volunteers to confirm the results of the single dose trial and to determine whether mesna dose schedules could be derived from the single dose trial. The IV schedule (600 mg three times daily at 0-8 hours after ifosfamide) was compared to 2400 mg of mesna film-coated tablets (300mg) once daily given at-1hr, 1200 mg twice daily given at-1hour and 4 hours, and a combination of iv and oral mesna (600 mg given IV and 1200 mg given po once daily at 0 ours). There was a 5-7 day interval between treatments.

Skin reactions (rash, erythema, pruritis, and flushing) were the most common ADE's noted, followed by nausea, abdominal colic, diarrhea and flatulence. One patient developed bronchospasm and retreatment was followed by urticaria. Three patients suffered rash, pyrexia, lethargy, headache and nausea.

With respect to PK, the excretion of mesna, dimesna and subsequent total thiols was slightly higher on day 5 than day 1 of the oral regimens. No accumulation in plasma was noted. During this study it was discovered that long term storage of film-coated tablets resulted in hardening of the tablet and decreased dissolution.

#### **6.2.1.4. D-07093-0017-Single Dose Bioavailability Study of Mesna 400mg Tablets**

This study was a single dose bioavailability study performed in 25 subjects with the objective of determining the bioavailability of 400 mg film-coated tablets with an iv injection of mesna as well as the

relative bioavailability of 400 mg film-coated tablets, 300 mg of film-coated tablets, 600 mg mesna tablets and mesna as an oral solution. The study was a 5-way crossover study in healthy volunteers. The 5 treatment arms consisted of 1200 mg single oral dose as three 400 mg tablets, 1200 mg single oral dose as four 300 mg tablets, 1200 mg single oral dose as two 600 mg tablets, 1200 mg single oral dose as 100 mg/ml injection solution given po, and 100 mg/ml mesna iv as an infusion of 600 mg. Blood and urine samples were collected at appropriate times.

Safety analysis indicated one subject withdrew secondary to loose stools, nausea, abdominal pain, rectal burning, vomiting and inability to eat. Other ADR's included rash, nausea, diarrhea, headache, and dizziness.

Plasma PK evaluation indicated that the AUC's did not differ significantly between the four groups administered as oral formulations of 1200 mg. The oral AUCs were approximately twice those observed after iv administration of a 600 mg dose. The plasma levels of both mesna and dimesna were similar in the different treatment groups. The AUCs observed after oral dosing (1200mg) were more than twice those observed for the iv (600 mg ) treatment.

Urinary excretion profiles of mesna mimicked the plasma concentration profiles of the corresponding route of administration. The cumulative urinary excretion (CUE) of mesna in mmol was similar in the po treatment groups. When compared to iv dosing, all oral doses appeared to result in greater CUE's. The cumulative urinary excretion of mesna over 36 hours of the 400 mg tablets were comparable to the other oral treatments for mesna urinary bioavailability since the 90% confidence limits of the CUE parameters for the 400 mg tablets were all within 80-120% of the other oral treatments. The 300 mg tablets were all comparable to the iv solution administered orally. The Rmax was also found to be comparable between oral dose forms. The iv treatment did not result in any measurable urinary levels of dimesna after 9 hours, but the oral treatments resulted in low but measurable urinary levels of dimesna in many subjects for at least 2 hours. The oral vs iv ratio of urinary bioavailability of mesna equivalents up to 36 hours is approximately 96%.

#### **6.2.1.5. D-07093-0015-Effect of Food on Urinary PK Study**

This was a Phase 1 open, single-center, randomized 4 way cross-over study consisting of the administration of 1200 mg mesna iv in the fasting state, two 600 mg tablets fasting, two 600 mg tablets given 30 minutes after breakfast, and 1200 mg orally administered

as the injection solution fasting. The objective was to define the urinary excretion and bioavailability of the single oral and iv doses of mesna given to 12 healthy volunteers. Urine samples for assay were collected at appropriate times. Four subjects sustained headaches, myalgia, arthralgia, pyrexia, shivering and flushing. Two subjects had a drop in lymphocyte counts 24 hours after dosing. During the first three dosing intervals, there was a transient fall in mean lymphocyte count in all 17 subjects (subjects replaced dropped outs). All changes in lymphocyte counts were transient and reversible. Headache was the most common ADR. Abdominal pain was reported in at least one patient in each group. Skin rash was most frequently reported in the iv group.

An evaluation of urinary PK indicated that the values of urinary recovery of mesna and dimesna were comparably low. There were no significant differences in the urinary excretion or absolute urinary bioavailability of mesna, dimesna and total thiols between the [redacted] tablets administered in the fed or fasted condition, or the orally administered injection solution. The bioavailability of free mesna in the urine after oral administration of mesna compared to iv mesna was 47.5% (tablet, fasted), 45.6% (tablet, fed), or 56.3% (oral injection solution, fasted), respectively. It would appear that food did not significantly affect the absorption of the [redacted] coated tablets. There were no significant differences in the absolute urinary bioavailability of total thiols when the [redacted] tablet was given under fasted or fed conditions.

#### **6.2.1.6. Comparison of Adverse Experience Profile of IV and Oral Administration in Volunteers**

Three previously reported studies were performed in the 1970's to assess the safety of mesna in volunteers. In the first study, single doses of 20, 30, and 40 mg/kg were administered to groups of healthy male volunteers.

Bad taste and soft stools in five of the six volunteers without changes in EKG, U/A, clinical chemistries, or hematology values were noted. In a second study three repeated injections, four hours apart of 20 and 30 mg/kg were given to 2 groups of adults. Again bad taste was reported along with a slight rise in blood pressure and soft stools in two of the subjects with no other effects on vital signs, EKG, U/A clinical chemistry, or hematology values. In a third study, 6 healthy male volunteers received doses of 60 mg/kg iv, 60 mg/kg po, and 70 mg/kg po on four consecutive days. In this study, there was a slight fall in weight, and a fall in BP with no clinically significant changes in EKG or clinical chemistry, except a fall in triglycerides on days 3 and 4. Diarrhea was reported by 4/6

subjects, fatigue by 4/6, limb pain by 3/6, as well as one episode each of nausea, pallor, and cardiovascular collapse (apparently not related to mesna). The adverse effect profile in phase I studies was similar for 1200 mg of orally administered iv solution, for 600-2400 mg po mesna tablets, as well as for 600 mg and 1200 mg iv mesna.

#### **6.2.1.7. Literature References**

The sponsor in the previous submission provided a review of 75 pertinent literature references published between 1981 and 1996, dealing with the utilization of oral mesna (given in various forms), in adequate as well as inadequate protective doses in man in which mesna was administered for uroprotection. These selected and uncontrolled human studies utilizing various forms of oral tablets (generally of an unstated formulation) or of a dissolved iv formulation demonstrate the relative efficacy of oral mesna in preventing the urotoxicity of ifosfamide. This overview represents a fairly large experience over many years in numerous countries as reported by a multitude of investigators and adds a supportive literature base for efficacy and safety. Though most authors and the sponsor fail to specify the formulation used, other data presented demonstrate the similarity of the various forms of mesna-iv solution, . . . tablets and . . . tablets. See Section 4.4

#### **6.2.1.8. Controlled Clinical Studies Previously Submitted**

There were three previously submitted controlled studies. Tables 3 and 4, adapted from the sponsor's previous submission, summarize the three randomized studies. Table 3 summarizes the types of studies and design features, and Table 4 the treatment details and major efficacy outcomes. Study D-07093-0019, while randomized and controlled was primarily a PK study, which called for a cross-over within cycle for patients on each of the mesna regimens, and thus does not permit direct comparison of the uroprotection of these regimens.

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**Table 2: Controlled Studies: Types of Studies and Design Features**

Protocol # Investigators	Type of Study	Comp date	Location	Study Design	Treatment	No. entered each treat.	Age range (mean)	M/F
<i>Controlled Clinical Studies</i>								
D-07093-0018 Multicenter	PK, efficacy, patients	Ongoing interim analysis Dec 1996	US	open, controlled, randomized cross-over	400 mg tablets, injection sol. iv	iv: 58 iv+po: 60	23-80 (58)	32/34
MED504 Multicenter	efficacy, patients	1996	Germany	open, randomized controlled, parallel	400 mg tablets, injection sol. iv	iv: 27 iv+po: 25	19-73 (52)	32/20
D-07093-0019 Johnson single center	PK, efficacy, patients	1993	US	open, controlled, randomized cross-over within cycle	300 mg tablets, injection sol. iv	13	40-79 (60)	13/0

**Table 3: Controlled Studies: Major Efficacy Outcomes**

Study	Ifosfamide Dose	No. Pts randomized to each Means Sequence	No. of Dropouts in each Sequence	Major Efficacy Outcomes
<i>Controlled Clinical Studies</i>				
D-07093-0018 Multicenter	1.2 - 2.0 g/m <sup>2</sup> daily over 3-5 days	iv+po/iv: 33 iv/iv+po: 33	9/7	Incidence of maximum grade of hematuria (RBCs/hpf); incidence of hematuria > 50 RBCs/hpf
MED504 Multicenter	2.0 g/m <sup>2</sup> daily over 5 days	iv/iv/iv: 27 iv/po/po: 27	3/3	Maximum number of RBCs/ul by FRC photo-count, direct microscopic count, sediment analysis, and dipstick
D-07093-0019 Johnson single center	1.2 g/m <sup>2</sup> daily over 5 days	iv/po/po: 7 (cycle 1&2) iv/iv/iv: 6 (cycle 1); 1 (cycle 2)	0/5	Any evidence of hematuria as measured by urine sediment (RBCs/hpf)

Tables 5 and 6 summarize respectively the same parameters for the uncontrolled studies. The two controlled studies were reviewed previously, as were the uncontrolled studies. They will only briefly be summarized.

**Table 4: Uncontrolled Studies: Types of Studies and Design Features**

Protocol # Investigators	Type of Study	Comp date	Location	Study Design	Treatment	No. entered each treat.	Age range (mean)	M/F
D-07093-0016 Multicenter	efficacy, patients	1994	Germany	open, uncontrolled	600 mg tablets, injection sol. iv	188	23-75 (58)	139/49
MED700 Multicenter	Efficacy, patients	1996	Germany	open, uncontrolled	400 mg tablets	31	21-74 (54)	24/7
MED200 Single center	efficacy, patients	1992	Switzerland	open, uncontrolled cross-over within cycle	300 mg tablets, injection sol. iv	11	25-77	6/5

**Table 5: Uncontrolled Studies: Major Efficacy Outcomes**

Study	Ifosfamide Dose	No. Pts randomized to each Mesna Sequence	No. of Dropouts in each Sequence	Major Efficacy Outcomes
<i>Uncontrolled Clinical Studies</i>				
D-07093-0016 Multicenter	1.2 - 2.5 g/m <sup>2</sup>	iv/po/po: 188	18	No macrohematuria; 8/188 (4%) severe hematuria (> 50 RBCs/hpf)
MED700 Multicenter	1.2 - 2.0 g/m <sup>2</sup> daily over 3-5 days	po/po/po: 31	2	No macrohematuria or severe hematuria observed
MED200	1.5 g/m <sup>2</sup> daily over 5 days	iv/po/po: 11	3	No case of hematuria ≥ 5 RBCs/hpf

**6.2.1.9. Study D-07093-10018 (as previously submitted)**

Open label, randomized, comparative 2-way cross-over study of the efficacy and safety of an iv and iv/oral regimen of mesna in patients treated with ifosfamide.

Out of a planned 120 patients, 66 patients were enrolled and randomized. The objective of the study was to compare the clinical efficacy of the two regimens in the prevention of ifosfamide-induced severe hematuria, and to compare the safety and tolerability of the two regimens (later amended to include collection of comparative PK data for mesna and dimesna). Patients received iv mesna at 60% of the ifosfamide dose and oral mesna at 100% of the ifosfamide dose as (20% iv followed by 40% and 40% of the iv dose po at 2 and 6 hours after ifosfamide administration.) Patients then received the alternate treatment for the second cycle. Study endpoints consisted of the incidence of severe hematuria, and safety and tolerability.

An intent-to-treat analysis was conducted by the Agency. With an approximate loss of 41% of patients, a crossover study analysis was not thought to be valid. As most patients completed the first cycle of the study, the Agency performed an analysis based on the first cycle data only. Those patients who discontinued prematurely were counted as successes if no events were observed in the first cycle. The results indicated that the incidence of Grade III or IV hematuria in the iv+po sequence was 1/33 (3%) and also 1/3 in the iv group, with a 0%. This suggested that the two treatment groups were essentially equivalent. One of the study centers failed to comply with good clinical practice per DSI inspection. When that center's patients were excluded, the upper bound of the 95% confidence limit was greater than the required 10% and the study was deemed not to demonstrate the statistical equivalence of the two regimens. Nevertheless only one patient actually had severe hematuria in any of the analyses.

There was a concern that there was a significant incidence of death on the iv+po arm. This was not explained and may have arisen by chance. A higher death rate was not seen in the second controlled study.

#### **6.2.1.10. Study MED504**

**European Multicenter Randomized Parallel Group (Phase III) of the Efficacy and Safety of Two Regimens of Mesna in Patients Treated With Ifosfamide.**

This randomized, multicenter, parallel group study with active control was performed in 11 centers in Germany. The objectives of the study were to compare the uroprotective efficacy of mesna by the approved iv regimen (three iv mesna doses equal to 20% of the ifosfamide dose given at 0, 4 and 8 hours) with an iv+po regimen in which the last two doses of the iv regimen were replaced by oral mesna tablet doses equal to 40% of the ifosfamide dose at 2 and 6 hours after ifosfamide dosing. The secondary objective was to compare the safety and tolerability of the two mesna regimens.

The primary endpoint of efficacy was defined as the maximum number of RBCs/ul in urine detected during the last 4 days of a 5-day course of ifosfamide and the 5 days post-treatment follow up (> than or < than 100 RBCs/ul). The secondary outcome parameters of efficacy were the maximum number of RBC's in the urine (RBCs/ul on days 2-10) based on direct microscopic counting. The primary outcome measures of safety consisted of adverse events, laboratory test results, and vital sign data.

In the final analysis, the many protocol violations were an issue. Of 52 patients, only 18 subjects in the iv group and 19 subjects in the iv/po group were included in the per-protocol analysis (15 subjects: 9 patients on the iv/iv/iv and 6 on iv/po/po were excluded from the intent-to-treat analysis). Also, in the Agency analysis, it was felt that the urine RBC concentration should be considered a continuous parameter since the maximum number of RBCs/ul for approximately 50% of the patients was below the limit of detection.

In the sponsor's evaluation, in both the intent-to treat and per-protocol population, 22% of the patients in the iv/iv group and 5% of the patients in the iv/po group had maximum RBC counts in the urine over 50 RBCs/ul (abnormal levels). Analysis by the FDA felt that the statistical

methodology used by the sponsor (Wilcoxin-Mann-Whitney test) was invalid. Analysis by the FDA utilizing the more appropriate Fisher's exact test for both populations showed that the mesna iv/iv and iv/po regimens were equally effective (Table 7). Though the study was flawed with respect to missing data and dropouts, it supports the uroprotective equivalence of iv+po mesna vs iv mesna alone.

**Table 6: Confidence Intervals for Frequencies of Hematuria Events\* - Intent-to-Treat and Per-Protocol Populations (FDA Analysis)**

Analysis	Incidence of Hematuria (Levels III and higher*)			95% 2-sided confidence bound and p-value
	iv/po/po	iv/iv/iv	Difference	
Intent-to-treat	1/23 (4.3%)	6/27 (22.2%)	-18%	(-40%, 4%) p=0.106**
per-protocol	1/19 (5.3%)	1/39 (2.2%)	-17%%	(-44%, 10%) p=0.18**

\*Level III = 50 to <100 RBCs/ul; Level IV = 100 to <500 RBCs/ul; Level V = 500 to <1000 RBCs/ul; Level IV = >1000 RBCs/ul

\*\*Smaller p-value indicates that iv/po/po regimen has better uroprotective effect

In this study, contrary to the previous study (D-07093-0018), in which there were 4 deaths in the po arm and none in the iv arm, there were 3 deaths in the iv/iv/iv arm vs. one death in the iv/po/po arm. Thus the concern that the po administration of mesna may be enhancing toxicity is somewhat assuaged.

## 6.2.2. Uncontrolled Studies Previously Submitted

### 6.2.2.1. Study 007093-0019

This open label, randomized, crossover within cycle, single-center study was conducted to assess urinary PK equivalence of two dosing regimens of mesna (iv only vs iv+po) given to cancer patients receiving ifosfamide. Of the 13 patients enrolled (7 in the iv+po arm and 6 in the iv only arm), there were 5 dropouts in the iv arm. In this underpowered and inadequately conducted study secondary to dropouts, no patient experienced above Grade I hematuria. The Biopharmaceutics reviewer concluded that the cumulative urinary excretion of the iv plus oral dosing regimen was similar to the iv reference regimen. The plasma PK data was

felt not to be reliable secondary to the small number of patients and the limited number of observations. In addition, the study did not use the to-be marketed preparation. This study provided limited support of safety and efficacy.

#### **6.2.2.2. Study 07093-0016**

This study was a Phase II trial designed to evaluate the uroprotective effect of mesna . ——— film-coated tablets (600 mg). It was an open label, uncontrolled, multicenter trial performed between 1992 and 1994 in a planned 88 subjects with the objectives of evaluating the uroprotective effect of mesna when administered as a combination of injection and film-coated tablets and assessing the tolerability of that mesna regimen.

No patient developed macrohematuria. There were 7 patients who developed Grade III microhematuria and 12 patients who developed Grade II microhematuria. The study was flawed by the fact that the tablets used were not of the same strength as the tablets proposed for marketing, the methodology for evaluating hematuria during the study differed from the controlled US study, and the number of inevaluable patients secondary to incomplete urinalysis was unacceptably high. The study lends modest support for the uroprotective effect of oral mesna.

#### **6.2.2.3. Study MED700**

This study was an open label, multicenter trial performed in 7 German centers designed to evaluate the uroprotective effect of mesna when given as 400 mg . ——— tablets only po/po/po, and to evaluate the safety and tolerability of this mesna regimen. Only 16 of the 31 patients entered were available for the per-protocol analysis of hematuria. The study was confounded by the fact that 9 patients received N-acetylcysteine for pulmonary reasons. No macrohematuria or severe microhematuria (>50 RBCs/hpf) occurred in the study. This poorly executed study, flawed by a large number of dropouts and confounded by the use of N-acetyl-cysteine, provides only borderline support of po mesna in preventing ifosfamide-induced hemorrhagic cystitis.

**6.3 Sponsor's Protocol-D-07093-3126 (3126)-Pharmacokinetics of Mesna, Dimesna and Ifosfamide After an IV and IV/Oral Regimen in Patients Treated with Ifosfamide: Multicenter, Open Label, Randomized, Multiple Dose, 2-Way Crossover Study.**

**6.3.1. Protocol Review**

**6.3.1.1. Objectives**

The primary objective of the study was to investigate the pharmacokinetics of mesna and its metabolite, dimesna, in blood and urine following administration of an iv or iv/oral regimen in ifosfamide-treated patients. The US approved regimen (3 doses each at 20% of the ifosfamide dose given at time 0, 4, and 8 hours) was compared with a proposed regimen of iv plus oral administration (20% of the ifosfamide dose given iv at 0 h; 40% of the ifosfamide dose given orally at 2 and 6 h).

The secondary objectives included the PK of ifosfamide in blood, as well as safety (including hematuria) and tolerability of the mesna treatment schedules.

The study was additionally designed to supplement study D-07093-0018 that was deemed insufficient in its previously submitted form.

**Study Design-**The study is a multiple dose PK study in a population of patients receiving ifosfamide (originally chosen to be patients with histologically confirmed sarcoma). It was planned as an open label, randomized, 2-way crossover trial in a total of 12 evaluable subjects (M and F). Treatment arms differed only in the order in which subjects received the oral or iv mesna accompanying the ifosfamide. Patients had to be scheduled to receive at least two cycles of chemotherapy with ifosfamide, with identical dose regimens in both cycles. The second cycle had to follow the first cycle within 3-8 weeks, allowing for recovery from cytotoxic therapy. Each cycle consisted of 5 consecutive days during which ifosfamide was administered once daily with a dose of 2.0 g/m<sup>2</sup>. The dose of mesna was adjusted in relation to the ifosfamide dose according to the following schedule:

**Table 7: Mesna Dose in % of Ifosfamide dose**

<b>Treatment</b>	<b>0 hour</b>	<b>2 hour</b>	<b>4 hour</b>	<b>6 hour</b>	<b>8 hour</b>
Iv/iv/iv	20% iv		20 % iv		20% iv
Iv/oral/oral	20% iv	40%		40%	

**6.3.1.2. Schedule of Tests**

Blood and urine samples for mesna, dimesna and ifosfamide assays were to be taken at specified intervals on days 1-5 of each cycle, and an additional blood sample was taken on day 6 for drug assay.

Data concerning the safety and tolerability were obtained by clinical surveillance and by monitoring of adverse events, blood pressure, heart rate and laboratory tests (hematology, clinical chemistry and urinalysis) during the course of the of the cycles.

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**Sponsor Table 8: Time Schedule**

	Pre Cycle	Pre Cycle	Treatment cycles 1 and 2-3-8						Post Cycle
	1	2	weeks apart form each other						2
Days	#	#	1	2	3	4	5	6	#
Ifosfamide			X	X	X	X	X		
Mesna			XX	X	X	X	X		
Informed consent	X								
Medical History	X								
Update Medical History		X							
Physical Examination	X								X
Vital signs	X	X	X	X	X	X	X		X
Performance Status	X	X							XX
Hematolgy,HCT									X
Clinical chemistry, Creat.	X	X	X				X		X
Urinalysis	X	X	X	X	X	X	X		X
Serum Pregnancy test	X	X							X
Urine Pregnancy test			X						
Blood sampling for Test Drug Assay			X	X	X	X	X	X	
Urine Sampling for test Drug Assay			X	X	X	X	X	X	
AE Observations	*any time during study	*	*	*	*	*	*	*	*

**6.3.1.3. Inclusion Criteria**

Subjects must have/be

- M/F, age 18-75
- Histologically confirmed malignancy
- Scheduled to receive two cycles of chemotherapy
- ECOG PS equal to or > 2
- Signed informed consent

#### **6.3.1.4. Exclusion Criteria**

Subjects must not have/be:

- History of allergic reaction to mesna or othr thiol containing drugs or ifosfamide
- Patients with autoimmune isorders
- Hb < 9 g/dl
- Hematuria
- Employ adequate birth control
- Positive pregnancy test
- Conditions that might interfere significantly with the absorption or distribution and elimination of mesna or cause increased risk of hematuria
- Severe impairment of renal and hepatic function (CrCl < 40ml/min, SGOT or SGPT > 2 fold over normal range.
- Severe impairment of cardiac, endocrine, pulmonary, gastrointestinal, neurological function, non-cancer related inflammatory process.
- Other chemotherapy within 3 weeks of study entry.
- Concomitant treatment: use of any drug thrapy that can interfere significantly with the absorption, distribution, elimination and determination of mesna, or cause an increased risk of hematuria, or interfere with the urinalysis (anticoagulants, cysine, cysteine, N-acetyl-cysteine).
- Exposure to another investigational agent within the last 30 days.
- Patients with a history of drug and/or alcohol abuse during the last 12 months.
- Appropriate administrative reasons (noncompliant, etc)

#### **6.3.1.5. Criteria for Removal**

- Lack of Efficacy
- Lack of tolerability
- Intercurrent disease
- Withdrawal of consent, noncompliance, change in treatment etc.

#### **6.3.1.6. Criteria for Evaluation**

1. Mesna and dimesna in plasma the last day: Area under the curve from 0-12 hours(AUC0-12), Area under the curve from 0-24 hours (AUC0-24), Mean Residence Time (MRT)
2. Mesna and dimesna in plasma on the last day: time at which maximal concentration occurs (Tmax) and point of maximal concentration (Cmax),
3. Mesna and dimesna in plasma: pre-dose levels on days 2 to last day
4. Mesna and dimesna in urine on day 1 and last day: Cumulative urinary excretion at times 12 hours and 24 hours-CUE 12h, CUE 24 h, Maximum and minimum rates of urinary excretion-Rmax, Rmin
5. Mesna and dimesna in urine on last day: renal clearance
6. Mesna and dimesna in urine: pre-dose levels on days 2 to last day
7. Ifosfamide in plasma on last day: AUC0-∞, AUC 0-12, AUC 0-24m Cmax, t1/2, Vz, Clearance, MRT
8. Ifosfamide in plasma: pre-dose levels on day 2 to last day
9. Maximum grade of hematuria based on erythrocyte counts in urine sediment.
10. Adverse events, laboratory tests, vital signs

#### **6.3.1.7. Statistical Methods (per protocol)**

1. Two sided 90% confidence interval for ratio of the two schedules based on multiplicative ANOVA model with factors of mesna schedule, cycle sequence and sample statistics.
- 2,3,6 Calculation of sample statistics
- 4 Two sided 90% confidence interval for ratio of the two schedules based on multiplicative ANOVA model with factors of the mesna schedule, cycle, day, day\* schedule, sequence, patient sequence and repeated measurement structure for day with "compound symmetry" covariance structure within periods.
- 5 Two-sided 90% confidence interval for ratio of parameters of the two schedules based on multiplicative ANOVA model with factors of mesna schedule, cycle, sequence, and patient sequence.
- 7 Two-sided 90% confidence interval for ratio of parameters of the two schedules based on multiplicative ANOVA model with factors of mesna schedule, cycle, sequence, and patient sequence.

- 8 Two-sided 90% confidence interval for the ratio of parameters of the two schedules based on multiplicative ANOVA model with factors of mesna schedule, cycle, day, day\* schedule, sequence, patient sequence and repeated measurement structure for ay with “compound symmetry” covariance structure within periods.
9. Shift tables for intra-patient comparison.
10. AE’s: Calculation of incidences, laboratory tests and vital sign: screening for remarkable changes and calculation of sample statistics.

### 6.3.2. Results of Study

### 6.3.3. Enrollment, Disposition, Demographics, Patient Characteristics

A total of 17 patients with a diagnosis of sarcoma were randomly assigned to one of the two study treatments. One patient was randomized but did not receive protocol therapy. As a result of major protocol deviations, two patients from each assigned sequence group were excluded from the per protocol analysis. In three cases (Patients-1/4, 1/7, and 1/35), the subjects had not completed both treatment cycles. One other patient (Patient 3/5) had had protocol violating stomach surgery, potentially interfering with the absorption of the study medication.

**Sponsor Table 9: Disposition of Patients Randomized**

	Disposition N of Patients		
	IV +PO/IV	IV/IV +PO	Total
Screened	10	8	18
Randomized	10	8	18
Not Exposed	1 (pt# 1/64)*		-1
Safety Population	9	8	17
Major Protocol Violation	-2	-2	-4
PP	(#1/4,1/7) 7	(#1/35,3/5) 6	13

# 1/64-did not comply with baseline eligibility criteria -preexisting hematuria, effusions

A total of 3 patients discontinued study treatment early as shown in Table 10.

**Sponsor Table 10: Premature Discontinuation**

	N of Patients	
	IV+ PO/IV	IV/IV +PO
Safety Population	9	8
-due to lack of efficacy (of chemotherapy; Pt#1/35 showed progression of disease)	1	
-Due to lack of tolerability (#1/4, 1/7)- chemotherapy intolerance, oral mesna intolerance	2	

Four patients were excluded from the ITT population because of major protocol violations (Table 11).

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**Sponsor Table 11: Major and Minor Protocol Violation**

<b>Minor protocol Violations</b>	<b>Treatment Sequence</b>	<b>Patient #</b>	<b>Actual Finding</b>
Other chemo-Therapy within 3 weeks of entry		1/37	Last chemotherapy (adria, ifos) 14 days before study
Anticoagulants within 10 days prior to and during any treatment cycle	IV +PO/IV	1/11	Lovenox before and during IV and IV+PO cycles
	IV +PO/IV	1/37	"
	IV/IV+PO	3/3	"
	IV/IV+PO	3/8	Coumadin at day 5 of IV+PO cycle
Hematuria at baseline (>50 erythrocytes/hpf in urine sediment	IV +PO/IV	3/10	114 rbcs/hpf in urine sediment 9 days before study entry but 5-10 rbcs/hpf 2 days before study entry
<b>Major protocol violation leading to exclusion from PP analysis</b>	<b>Treatment Sequence</b>	<b>Patient</b>	<b>Actual Finding</b>
Premature discontinuation (did not complete 2 cycles)	IV+PO/IV	#1/4	Discontinuation after day 0 Of 2 <sup>nd</sup> cycle
	IV+PO/IV	1/7	Discontinuation after day 1 of 1 <sup>st</sup> cycle
	IV/IV+PO	1/35	
Condition that interferes with absorption of mesna	IV/IV+PO	3/35	Resection of stomach

## Demography

**Sponsor Table 12: Patient Demographics**

		Treatment Sequence		Total
		IV +PO/IV	IV/IV+PO	
		N=9	N=8	
<b>Sex</b>	<b>Male</b>	2	5	7
	<b>Female</b>	7	3	10
<b>Race</b>	<b>White</b>	9	7	16
	<b>Black</b>	0	1	1
<b>Age (years)</b>	<b>Mean</b>	39.3	47.4	43.1
	<b>SD</b>	=/-10.2	=/-20	=/-15.6
	<b>Median</b>	37	51	40
	<b>range</b>	25-57	19-74	19-74
<b>Weight (kg)</b>	<b>Mean</b>	71.6	76.4	73.9
	<b>SD</b>	=/-20.9	=/-18.6	=/-19.4
	<b>Median</b>	65.3	73	70.2
	<b>Range</b>	52-117	52-99	52-117

All patients had sarcoma. Fourteen of the 17 patients had received prior therapy for their sarcoma. The majority of patients had undergone surgery and/or chemotherapy. Twelve patients had received chemotherapy. Fifty-nine percent of patients (10) had WHO PS 0, 35% WHO PS 1 (6) and one evaluation was missing.

Concomitant medication used in 3 or more of patients were summarized by the sponsor (Tab 8; List C11, Volume 4, Page 50). Antiemetics and anti-nauseants, plasma substitutes and perfusion solutions, antacids, drugs for treatment of peptic ulcer and flatulence, laxatives, stomatological preparations, psycholeptics, analgesics, psychoanaleptics, mineral supplements, diuretics, systemic antibacterials, antithrombotic agents, vitamins, corticosteroids, dermatological preparations, thyroid therapy, immunomodulating agents, antiinflammatory and antirheumatic products and topical products for joint and muscular pain were well matched (n=156 in both the IV+PO cycles and IV only cycles)

### 6.4 Hematuria

The incidence of hematuria was summarized for each mesna regimen using the grading scale in Table 13. All sediment results (local and central laboratory) were used to select the maximum grade of hematuria per treatment cycle.

**Sponsors Table 13: Hematuria**

Erythrocytes in urine sediment		Grading
Counts (cells/hpf)	Verbal classification	
0-20	Negative, none, trace, occasional	Grade I
21-50		Grade II
>50		Grade III
# (too numerous to count)	Visible blood, hematuria	Grade IV

Shift tables for an intra-patient comparison between cycles and mesna schedules are summarized in Table 14.

**Sponsor Table 14: Hematuria**

		N of Patients					
		Schedule IV					All
		Grade I	Grade II	Grade III	Grade IV	Missing	
Schedule IV +PO	Grade I	9	1	0	1	1	12
	Grade II	2	1	0	0	0	3
	Grade III	1	0	0	0	0	1*
	Grade IV	0	0	0	0	0	0
	Missing	1	0	0	0	0	1
	All	13	2	0	1**	1	17

\*Patient 1/6 had a Grade III hematuria on day 2 of the first cycle (IV+PO) according to the sediment analysis of the center laboratory (50-75 RBCs/hpf). The central lab result for the same day was negative.

\*\* Patient 3/8 had a Grade IV hematuria at day 6 of the first cycle (IV schedule) In the second cycle (IV+PO schedule) hematuria was Grade I.

Hematuria was reported as an AE in 6 patients after the administration of the IV+PO schedule and in 5 patients after application of the IV schedule. Table 15 describes a cross reference between the AE reporting and the observed maximum grade of hematuria based on urine sediment analysis.

**Sponsor Table 15: Clinical Trial Center and Sediment Analysis Cross Reference**

Patient	Schedule	Intensity of AE*	Sediment analysis
1/4	IV+PO IV	CTC grade 2 CTC grade 1	Grade II Grade I
1/9	IV+PO	CTC grade 1	Grade II
1/12	IV+PO IV	CTC grade 1 CTC grade 1	Grade II Grade II
1/34	IV	CTC grade 1	Grade I
3/5	IV+PO	CTC grade 1	Grade I
3/8	IV+PO IV	CTC grade 1 CTC grade 2	Grade I Grade IV
3/10	IV+PO IV	CTC grade 1 CTC grade 1	Grade I Grade I

CTC 1=microscopic only

CTC2= intermittent gross bleeding, no clots

In study 3126, the incidence of hematuria was measured as a safety parameter. As this study was designed as a PK study, the study did not provide statistical consideration for efficacy. However, as the labeled indication for mesna is protection against ifosfamide induced hematuria, it was treated as a descriptive efficacy parameter.

Review of this efficacy parameter was conducted by this medical officer and the biometrics reviewer. Data was included from both treatment sequences. There was one patient (patient 3/8) who sustained Grade IV hematuria on day 6 of the first treatment cycle during which mesna was given by the iv/iv/iv schedule. In the following treatment cycle, when mesna was given in the iv/po/po schedule, the patient sustained only Grade I hematuria. Another patient sustained grade III hematuria (patient 1/6) on day 2 of the first cycle when mesna was given by the iv/po/po regimen. That subject showed Grade I hematuria in the second cycle in which mesna was administered by the iv/iv/iv scheme. These results support the similarity of uroprotection provided by both regimens. No statistical test was performed due to the limited number of patients, crossover design, and lack of prespecified test.

#### **6.4.1.1. Pharmacokinetic Results (See Biopharmaceutical review)**

The PK evaluations were performed for all available analytical data sets. Groupwise descriptive statistics of the PK parameters were used; however, only those patients who had crossed over to both ifosfamide/mesna regimens could be used for a PK comparison. In this study, patients were to be extensively hydrated, i.e., to receive at least 3 liters of fluid per day in both treatments. Of the 17 patients who received treatment, 4 were rejected from the PK evaluation for not having finished both treatment cycles (01-04, 01-07, and 01-35) or due to a major protocol violation for an oral medication (Patient 03-05, s/p gastrectomy). There were 13 evaluable patients, 8 of whom were female, whose age ranged from 19 to 63 years and body weights from 51.9 to 70.2 kg and 5 males whose age ranged from 40 to 73 years and whose body weight was 90.6 to 117 kg.

Per protocol, on day 5, C<sub>max</sub>, AUC<sub>0-last</sub> (area under the curve from time 0 to the last observation), AUC<sub>0-12</sub>, AUC<sub>0-24</sub>, AUC<sub>0-inf</sub> and T<sub>1/2</sub> (where possible) of mesna, dimesna, and ifosfamide were to be determined in plasma. In addition MRT, approximately as AUMC<sub>0-24</sub>/AUC<sub>0-24</sub> were to be determined, (particularly in the iv/iv/iv treatment regimen with mesna). T<sub>1/2</sub> for mesna and dimesna (and consequently AUC<sub>0-inf</sub>) could not be determined due to insufficient data sets in the terminal phase.

PK was evaluated non-compartmentally. Only patients who had completed both cycles could be investigated for a possible mesna PK difference. Thirteen patients who "crossed-over" provided the PK parameters.

##### **Mesna in plasma**

The plasma profiles of the iv/iv/iv schedule exhibited three peaks. After iv/po/po administration, one sharp peak from the iv dose and flatter oral plasma peaks were detected. Plasma T<sub>1/2</sub> could not be determined in all patients due to an insufficient number of measurable concentration values in the terminal portion of the plasma profiles. Consequently, total plasma AUC<sub>0-inf</sub> could not be estimated by extrapolation. In the 13 patients whose T<sub>1/2</sub> was evaluable, it varied from 1-8 hours.

After the three successive iv doses, plasma AUC<sub>0-24</sub>, equaled total plasma AUC<sub>0-inf</sub>, because from 12-24 hours there was no further AUC increase. The total AUC was used for the calculation of the total plasma clearance (CL<sub>mean</sub>): 0.44l/h/kg. The predose plasma concentrations of mesna day 1-5 of both regimens were essentially non-detectable or negligible, with no tendency for significant accumulation. The ratio of iv/po/po versus iv/iv/iv plasma AUC<sub>0-12</sub>, AUC<sub>0-24</sub>, and MRT was 1.11-1.49, 1.30-1.76, and 1.22-1.45 (90% confidence interval), respectively.

### **Dimesna in plasma**

The 13 crossover patients that were evaluable in both cycles provided PK parameters. The iv/iv/iv mesna regimen produced 3 sharp peaks whereas the iv/oral/oral regimen led to flatter peaks. Plasma half-life could not be determined in all patients due to an insufficient number of measurable concentration values in the terminal part of the plasma profiles (as above, AUC0-24 served as a surrogate). In those 13 patients whose plasma half-lives could be determined, it ranged from 2-10 hours.

The exposure (AUC) of dimesna after the iv/oral/oral schedule exceeded that after the iv/iv/iv regimen by nearly the same extent as found for the parent mesna. The plasma AUC of dimesna was about 70% of the mesna AUC. During the 5 day treatment with either schedule, the dimesna concentrations in the plasma mostly returned to undetectable or negligible concentrations by 24 hours (predose). No accumulation was detected. The ratio of iv/po/po versus iv/iv/iv AUC0-12, AUC0-24, and MRT was 1.3-1.55, 1.55-1.83, and 1.17-1.40 respectively (90% CI).

### **Ifosfamide in plasma**

Some analytical results were implausible (possible contamination -patient 01/37). From plasma profiles of the other plausible 12 patients, it was concluded that the maximum ifosfamide plasma levels were attained at the end of the 2h infusion and that thereafter the levels declined monoexponentially, without an indication of an initial distribution phase. It appeared on serial day 1-5 determinations that the carryover of ifosfamide plasma concentrations from the preceding day was decreasing, possibly due to enzyme induction. The PK of ifosfamide in the plasma are nearly identical in both mesna regimens (Table 16).

**Sponsor Table 16: Summary of Predose Plasma Concentrations of Ifosfamide after an iv/iv/iv an iv/oral/oral regimen in patients treated with ifos.**

<b>Ratios for the Ifosfamide Predose Plasma Levels (ANOVA)</b>				
	<b>Iv/iv/iv Day 5 vs day 2</b>	<b>Iv/oral/oral Day 5 vs day 2</b>	<b>Day 2 iv/oral/oral vs iv/iv/iv</b>	<b>Day 5 iv/oral/oral vs iv/iv/iv</b>
<b>N</b>	12	12	12	12
<b>Estimate</b>	0.22	0.34	0.8	1.24
<b>90% CI</b>	0.15-.34	0.23-0.52	0.52-1.25	0.8-1.94

### **Urinary PK**

Urinary PK of mesna and dimesna were evaluated on day 1 and 5 in both mesna dosing regimens. The CUE (cumulative urinary excretion) and

Ucum of mesna and dimesna (cumulative urinary amount of mesna and dimesna) at 12 h and 24 h were determined. Where possible, renal clearance was calculated.

### **Mesna in Urine**

The urinary concentrations after the iv/iv/iv schedule reflect the 3 peaks observed in the plasma over 24 hours. They are in the same order of magnitude on day 1 as on day 5. After the iv/po/po schedule, the first (iv) dose results in one urinary peak, whereas the two succeeding oral doses produce merged peaks. The concentration on days 1 and 5 are similar.

On days 1 and 5 of the two treatment schedules, urine fractions were collected, after which, PK analyses were performed. The total amount excreted was calculated, as per the study protocol, by plotting excretion rates vs the collection interval mid-times, and performing an AUC calculation for the curve with extrapolation to infinity. Due to the poor terminal fit quality of the data obtained, the information was felt to be unreliable. The data was in good agreement, however, with Ucum0-24 hours obtained by simply adding up the fractions (no relevant amounts are recovered beyond 24 hours).

The urinary mesna concentrations measured predose on days 2-5 through day 5 of the 5 day treatment are smaller in the iv/iv/iv schedule than in the iv/po/po schedule. During the 5 day treatment the predose levels exhibited some inter- and intra-individual variability on both treatment arms. No or only insignificant accumulation of urinary mesna concentrations may occur, with steady state rapidly attained. The ratio of the urinary mesna ratios after an iv/iv/iv on day 5 vs day 1 was 1.0, 1.01, .91 and 1.60 for Ucum0-12, Ucum 0-24, Rmax, and Rmin, respectively (90% confidence interval). The ratio of day 5 vs day 1 mesna after an iv/po/po regimen is 1.44, 1.140, 1.43 and 1.04 for the same parameters, respectively. The day 1 ratios for iv/po/po vs iv/iv/iv was 1.01, 1.23, .82, and 7.45, and the day 5 ratio of iv/po/po vs iv/iv/iv were 1.44, 1.71, 1.29 and 4.81, respectively, for the same values with a Clren (renal clearance) iv/po ratio on day 5 of 1.3.

Similarly for dimesna, the iv only patients rarely had measurable predose concentrations of dimesna in the urine. The values showed no tendency for a further increase during the 5 day treatment period

In the iv/po/po regimen, all patients had predose mesna concentrations remaining from previous po mesna administration in the urine. They were higher than in the iv only group and varied considerably within and between patients. No uniform trend for an increase was detectable during the 5 days and there were no or insignificant accumulations of urinary dimesna concentrations. Steady state was rapidly attained.

#### **6.3.2.4 Overview of Efficacy Data for Indication #1**

The issue of efficacy is essentially established by data submitted in the previous submission and study 3126. The resubmitted and reanalyzed study 0018 was supportive but remained dubious from the statistical and methodological standpoint

With respect to study 3126, the sponsor maintains that equal uroprotection is afforded by a combination of iv mesna followed by double dose mesna prescribed as an oral tablet at 2 and 6 hours after an iv dose of ifosfamide.

In the Agency biopharmaceutical analysis, Study 3126 demonstrated that the plasma AUC for iv/po/po regimen achieved a relative overcompensation of 129-151% compared to the alternative approved iv/iv/iv schedule. Only rarely was the trough level of mesna or dimesna in the iv/iv/iv regimen detectable, while it was detectable most of the time in the iv/po/po regimen. Similarly, urinary mesna excretion on days 1 and 5 indicated that the urinary levels of mesna on day 5 were higher than on day 1 for the iv/po/po schedule. This was not the case for the iv/iv/iv schedule. In addition, the urinary levels for mesna for the iv/po/po schedule are higher than that for the iv/iv/iv regimen (particularly on day 5) indicating an accumulation of mesna in plasma.

It was not clear if an elevated or prolonged exposure to mesna would effect ifosfamide PK. Review of the data showed that the PK profiles of ifosfamide were similar in the two regimens.

Lastly, Agency Biopharmaceutics exploratory PK/PD analyses demonstrated that exposures (AUC) were related to time to first occurrence of nausea (p value 0.026 for AUC) possibly explaining the higher incidence of nausea in the iv/po/po arm.

The Sponsor concluded that the iv/po/po regimen resulted in plasma peak concentrations at the same times as the conventional iv/iv/iv regimen, because the times of oral dosing accounted for a delayed t<sub>max</sub> compared to iv dosing.

The two oral mesna doses of the iv/po/po schedule were increased over the corresponding iv doses of the iv/iv/iv regimen to compensate for a decreased bioavailability by the oral route. In point of fact, there is an overcompensation that may be associated with a greater incidence of nausea and vomiting. The plasma peak concentrations were lower but longer lasting.

Accumulation of mesna in the plasma was either negligible or absent. This deviates from the Agency Biopharmaceutics review. The maximum mesna excretion rates attained in the urine were similar for both regimens (the

minimum rates observed at the end of the 24 hour cycle with the iv/po/po regimen were above the rates observed with the iv/iv/iv schedule).

No accumulation of mesna in the urine was seen after 5 days on the iv/iv/iv regimen, however, after the iv/po/po schedule, an accumulation of the urinary concentrations was observable. Its extent was small.

The PK of dimesna in the plasma was similar for both schedules. It was felt by the sponsor that the increased plasma AUC of the iv/po regimen derived from the higher po doses of mesna than in the iv only regimen. Some accumulation of urinary dimesna of the urinary concentrations of dimesna was seen in the iv/oral regimen.

The plasma PK of ifosfamide were nearly identical in both mesna regimens demonstrating that the two mesna regimens did not have an impact on ifosfamide PK.

The difference between the Agency evaluation and the Sponsor's evaluation was not significant from the PK standpoint except with respect to a greater Agency concern regarding the higher plasma AUC of oral mesna, the accumulation of plasma mesna on day 5, and the impact of those mesna concentrations on the early time course and incidence of mesna induced nausea that correlated with higher mesna AUC values.

It was suggested by Biopharmaceutics that the following information should be taken into consideration by the medical review staff:

1. Higher exposures of mesna for the iv/oral/oral regimen compared to the iv/iv/iv regimen were observed. In addition, accumulation in the iv/oral/oral regimen was evident.
2. The elevated exposures may not provide additional urprotection and clinical benefits.
3. The PK/PD analysis suggested that higher exposure caused higher probability of earlier occurrence of nausea.

#### **Mesna tumor protection.**

As the AUCs of plasma mesna were higher in the po regimen than in the iv only regimen, issues arise as to whether mesna either protects tumors from the tumoricidal effects of ifosfamide or combines with the active species or metabolite of ifosfamide to inhibit its efficacy. Ten preclinical studies, submitted in the 1988 submission (NDA 19-844) demonstrated that in animal tumor systems, utilizing variable doses of ifosfamide and mesna, there was no evidence that mesna inhibited response rates or tumor cure rates.

Thermodynamic and PK computer modeling and analysis by Agency Biopharmaceutics and by the sponsor indicated that the molar concentrations of mesna compared to the already available pools of sulfhydryl compounds in plasma were not likely to impede ifosfamide activity.

A retrospective review of human studies submitted in the 1988 NDA (19-884) also failed to indicate an inhibition of survival or or tumor control rate.

Lastly, newer studies utilizing high doses of ifosfamide (2-5 g/m<sup>2</sup>) with simultaneously administered equal doses of mesna given by continuous infusion continued to show high response rates.

Though definitive data is not available regarding tumor protection by mesna, the available weight of evidence indicates no preclinical, clinical or thermodynamic evidence of tumor protection.

#### **6.4.1 Conclusions for Efficacy for Indication**

Mesna given by either a iv/iv/iv or iv/po/po route of administration appears to provide comparable uroprotection against ifosfamide induced urotoxicity as demonstrated by incidence of hematuria. The oral route of administration using the recommended ratio of 40% of the ifosfamide dose provides higher plasma and urinary AUCs than an iv only mesna regime.

### **7. Integrated Review of Safety**

#### **7.1 Brief Statement of Findings**

The issue of uroprotection from ifosfamide-induced hematuria has been addressed above. With respect to other parameters of safety, the sponsor concludes that no major differences in tolerability were associated with the two different schemas of mesna administration. Toxicity is predominantly associated with the co-administration of the cytotoxic ifosfamide. Nausea, however, was more frequently observed after use of mesna in the iv/po/po dosing scheme (14/16 patients-88%) than after the iv/iv/iv regimen of mesna (9/16 patients-56%). In addition a marginally higher incidence of vomiting was noted after iv/po/po dosing of mesna (7 vs 5 patients). Of significance, one patient was actually withdrawn from the study secondary to vomiting shortly after ingesting mesna tablets. An integrated summary of safety based on 3126 and 3 additional controlled trials suggests a trend for more vomiting with po mesna but not nausea.

It was not always possible for investigators to separate the adverse effects of ifosfamide from that of mesna. However, in comparing the adverse events in both study arms, there appeared to be no significant differences in vital sign or laboratory parameters.

No deaths occurred on study. It was felt that the serious adverse events reported in the study were largely attributable to ifosfamide, including hematotoxicity, g.i toxicity, and CNS effects.

An important safety issue not addressed by the sponsor, was the occurrence of 3 cases of acidosis in the po arm vs. none in the iv only schedule. In one acidotic patient the acidosis was specifically attributed to the inability to ingest fluids secondary to nausea and vomiting (patient 01-04).

A review of the case report forms suggests a far greater incidence of acidosis in both arms of the study. No blood pH measurements were performed. If acidosis is defined by abnormally low CO<sub>2</sub> and/or inappropriately high urine pH in the circumstance of a low CO<sub>2</sub> (ifosfamide is associated with renal tubular acidosis- or a Fanconi-like syndrome), then seven patients had an "acidosis" in each arm. Of the 16 patients who received ifosfamide, 8 patients (01-04,01-02, 01-09, 01-65, 03-03, 03-05, 03-08,03-10) sustained acidosis by the above criteria. Six patients (01-09, 01-65, 03-03, 03-05, 03-08, 03-10), sustained acidosis in both arms of the study, one patient (01-02)sustained acidosis in the iv only arm, and one patient sustained acidosis in the po arm only (01-04).

The presence of acidosis associated with ifosfamide remains a potential safety issue. Product labeling does cite an incidence of renal tubular acidosis in up to one third of subjects receiving ifosfamide. Interestingly all patients treated at the Columbia University Study Center received iv sodium bicarbonate during their ifosfamide infusions. This practice suggests a lack of uniformity in ifosfamide/mesna usage.

There appeared to be no difference in the incidence of acidosis between the arms contrary to the sponsor's submission.

## **7.2 Materials Utilized in the Review-see efficacy review**

## **7.3 Description of Patient Exposure-see efficacy review**

## **7.4 Safety Findings From Clinical Studies**

### **Overview**

Table 17 represents the review summary findings of adverse reactions, which were reasonably associated with mesna administered IV and orally in four controlled studies (0018, MED504, 2 PK studies).

**Sponsor Table 17: Global Incidence of Adverse Events and Incidence of Most Frequently Reported Adverse Events in Controlled Studies**

Mesna regimen	i.v.	i.v.+ p.o.
N exposed-	119 (100%)	119 (100%)
Global incidence of AEs	101 (84.9%)	106 (89.1%)
Most Frequently Reported Adverse Events (Preferred Terms)		
	N (%)	N (%)
Nausea	65 (54.6%)	64 (53.8)
Vomiting	35 (29.4)	45 (37.8)
Constipation	28 (23.5)	21 (17.6)
Leukopenia	25 (21.0)	21 (17.6)
Fatigue	24 (20.2)	24 (24.2)
Fever	24 (20.2)	18 (15.1)
Anorexia	21 (17.6)	19 (16.0)
Thrombocytopenia	21 (17.6)	16 (13.4)
Anemia	20 (16.8)	21 (17.6)
Granulocytopenia	16 (13.4)	15 (12.6)
Asthenia	15 (12.4)	21 (17.6)
Abdominal pain	14 (11.8)	18 (15.1)
Alopecia	12 (10.1)	13 (10.9)
Dyspnea	11 (9.2)	11 (9.2)
Chest pain	10 (8.4)	9 (7.6)
Hypokalemia	10 (8.4)	11 (9.2)
Diarrhea	9 (7.6)	17 (14.3)
Dizziness	9 (7.6)	5 (4.2)
Headache	9 (7.6)	13 (10.9)
Pain	9 (7.6)	10 (8.4)
Sweating increased	9 (7.6)	2 (1.7)
Back pain	8 (6.7)	6 (5.0)
Hematuria	8 (6.7)	7 (5.9)
Injection site reaction	8 (6.7)	10 (8.4)
Edema	8 (6.7)	9 (7.6)
Edema peripheral	8 (6.7)	8 (6.7)
Somnolence	8 (6.7)	12 (10.1)
Anxiety	7 (5.9)	4 (3.4)
Confusion	7 (5.9)	6 (5.0)
Face edema	6 (5.0)	5 (4.2)
Insomnia	6 (5.0)	11 (9.2)
Coughing	5 (4.2)	10 (8.4)
Dyspepsia	4 (3.4)	6 (5.0)
Hypotension	4 (3.4)	6 (5.0)
Pallor	4 (3.4)	6 (5.0)
Dehydration	3 (2.5)	7 (5.9)
Pneumonia	2 (1.7)	8 (6.7)
Tachycardia	1 (0.8)	7 (5.9)
Flushing	1 (0.8)	6 (5.0)

Counts and incidence rates for preferred terms are ordered by the rates shown in the first column

**Study 3126**

The sponsor reports that only nausea occurred more frequently after administration of the IV+PO regimen; however, it is noted that acidosis occurred in three of the IV+PO subjects and none of the IV patient (See Medical Officer analysis above which corrects this to 7 patients in each arm). Table 18 demonstrates the most frequently TESS (treatment emergent sign and symptoms) occurring during the study.

**Sponsor Table 18: Incidence of Most Frequent\* TESS-(Treatment Emergent Signs and Symptoms) Sorted by Likelihood of being an ADR\***

WHO preferred Term	IV+PO schedule, N=16						IV schedule, N=16					
	L		L+N		L+N+U		L		L+N		L+N+U	
	n	%	n	%	n	%	n	%	n	%	n	%
Nausea	14	87.5	14	87.5	14	87.5	9	56.3	9	56.3	9	56.3
Fatigue	7	43.8	7	43.8	8	50	8	50	8	50	9	56.3
Constipation	4	25	4	25	7	43.8	2	31.3	5	31.3	5	31.3
Vomiting	6	37.5	6	37.5	7	43.8	5	31.3	5	31.3	5	31.3
Hematuria	5	31.3	5	31.3	6	37.5	4	25	4	25	5	31.3
Anemia	4	25	5	31.3	5	31.3	3	18.8	3	18.8	3	18.8
Insomnia	2	12.5	2	12.5	5	31.3	0	0	0	0	2	12.5
Pallor	3	18.8	4	25	4	25	2	12.5	4	25	4	25
Alpaca	3	18.8	4	25	4	25	2	12.5	2	12.5	2	12.5
Anorexia	3	18.8	3	18.8	4	25	3	18.8	3	18.8	4	25
Tachycardia	1	6.3	1	6.3	4	25	1	6.3	1	6.3	1	6.3
Edema	2	12.5	3	18.8	3	18.8	1	6.3	1	6.3	2	12.5
Acidosis	3	18.8	3	18.8	3	18.8	0	0	0	0	0	0
Back pain	0	0	0	0	3	18.8	0	0	0	0	1	6.3
Diarrhea	1	6.3	1	6.3	3	18.8	0	0	0	0	0	0
Granulo-Cytopenia	3	18.8	3	18.8	43	18.8	2	12.5	2	12.5	2	12.5
Somnolence	0	0	0	0	3	18.8	0	0	0	0	2	12.5

L-likely, N-not assessable or missing; U-unlikely; n-number of patients with that event

\* this table shows all terms that occurred in at least three patients of the IV+PO regimen

**\*\* sorted first by the L+N+U column of the IV+PO schedule**

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

Serious and other significant adverse events that occurred in 6 patients are shown in Table 19.

**Sponsor Table 19: Serious and Other Significant Adverse Events**

Patient	Schedule	WHO preferred term	Day	CTC grade	Causality	Outcome
1/2	IV+PO	Anemia	11	3	Likely	Resolved
		Granulocytopenia	11	3	Likely	Resolved
		Syncope	11	3	Likely	Resolved
		Thrombocytopenia	11	4	Likely	Not resolved
	IV	Anemia	66	3	Likely	Resolved
		Nausea		3	Likely	Resolved
1/4	IV+PO	Renal tubular disorder	5	3	Likely	Resolved
		Vomiting	6	3	Likely	Resolved
		Nausea	6	3	Likely	Resolved
		Hematuria	50	2	Unlikely	Resolved
	IV	Confusion	4	2	Likely	Resolved
1/11	IV+PO	Hypoxia	22	3	Unlikely	Resolved
		Dyspnea	22	3	Unlikely	Resolved
		Somnolence	22	2	Unlikely	Resolved
1/35	IV	Constipation	9	3	Unlikely	Resolved
		Back pain	9	3	Unlikely	Not resolved
3/3	IV	Leucopenia	12	3	Likely	Resolved
		Granulocytopenia	12	3	Likely	Resolved
3/8	IV	hematuria	6	2	Likely	Not documented

There were no deaths in the study. Two patients discontinued the study due to adverse events. One patient (#1/4 received the IV schedule), suffered confusion on day 4 (CTC toxicity of 2). The condition resolved but causality with the study medication was likely. Patient 1/7 allocated to the IV+PO regimen sustained vomiting on day 1. This condition resolved and causality was considered likely.

Review of sample statistics for changes of vital sign parameters during treatment days compared to baseline revealed a considerable increase ( $p < 0.5$ ) for systolic blood pressure at day 4 in the IV +PO cycle. The mean pressure at that time was 7.0+/- 11.0 mm HG. On the other hand, the post cycle values of blood pressure

and pulse rate after administration of the IV schedule were considerably higher as compared to baseline (Table 20).

**Sponsor Table 20: Notable changes in blood pressure and pulse rate**

Parameter	Number of patients with notable changes			
	IV+PO cycles N=16		IV cycles N=16	
	Decrease	Increase	Decrease	Increase
Systolic	1	1	3	2
Diastolic	6	3	3	2
Pulse rate	3	2	-	2
<b>Patients affected overall</b>	11		10	

It is not clear or explained why the BP elevations noted above are not reflected in the above table. Apparently increases and decreases appeared in both arms of the study.

Laboratory parameters were evaluated during four time windows designed to collect data from varying times using both local and central laboratories: baseline, days 2-10, days 11-20, and 21-30 (last value of multiple values per time period was utilized). See Table 21.

**Sponsor Table 21: Notable Differences of Laboratory Findings From Baseline (p value sign rank test < 0.05)**

Parameter group	Schedule	Parameter	Days	Mean difference to baseline	p-value rank test
Hematology	IV	Leukocytes	11-20	11.80 /nl	.016
	IV	Thrombocytes	2-10	-54.00 /nl	
Differential blood count	IV+PO	neutrophils	2-10	7.86%	.010
	IV	Lymphocytes	11-20	-9.30%	.031
	IV	monocytes	2-10	-4.26%	.007
	IV	Monocytes	11-20	-4.94%	.016
	IV	eosinophils	11-20	-1.80%	.016
Electrolytes	IV+PO	Sodium	2-10	-2.69 mmol/l	.001
Substrates	IV+PO	Glucose	11-20	-0.82 mmol/l	.031
	IV+PO	BUN	2-10		.002

Notable changes of hematological parameters (increase of a least one CTC grade of hemoglobin, leukocytes or thrombocytes) occurred in 10 of the IV+PO subjects and 9 of the IV subjects (no apparent difference). Four IV+PO patients had either increases or decreases of neutrophils, lymphocytes, monocytes, basophils, and eosinophils, while 6 IV patients had increases or decreases in those parameters. No specific clinical significance could be ascribed to small number differences of lymphocytes, monocytes, basophils or eosinophils. These changes are believed primarily due to the cytotoxic chemotherapy. There appeared to be no significant differences between the arms.

Two patients in the IV+PO schedule sustained a CTC grade increase of SGOT, SGPT or ALKP as compared with 6 patients receiving iv.

The issue of uroprotection from ifosfamide induced hematuria has been addressed in the discussion of efficacy. With respect to other clinical parameters, the sponsor concludes that no major differences in tolerability were associated with the two different mesna administrations. Toxicity is predominantly associated with the co-administered cytotoxic ifosfamide. Nausea, however was more frequently observed after the iv/po/po dosing scheme (14/16-88%) than after the iv/iv/iv regimen of mesna (9/16-56%). In addition, a marginally higher incidence of vomiting was noted after iv/po/po dosing of mesna (7 vs 5 patients). Of significance, one patient was actually withdrawn from the study secondary to vomiting shortly after ingesting mesna tablets.

## **7.5 Miscellaneous Studies**

None

## **7.6 Literature Review for Safety-See Section 4.3**

## **7.7 Post Marketing Surveillance**

Consultation for ODS was obtained. There is no need to change the label at this time. Current AEs included in the label as postmarketing reports are "allergic reactions, decrease of platelet count associated with allergic reactions, hypertension, hypotension, increased heart rate, increased liver enzymes, injection site reactions (including pain and erythema), limb pains, malaise, myalgia, ST-segment elevation, tachycardia, and tachypnea have been reported as part of postmarketing surveillance."

## **7.8 Safety Update-Not applicable.**

## **7.9 Drug Withdrawal, Abuse, and Overdose Experience-Not applicable.**

#### **7.10 Adequacy of Safety Testing**

The safety review was generally adequate.

#### **7.11 Labeling Safety Issues and Postmarketing Commitments**

None

#### **7.12 Biopharmaceutical Labeling Recommendations-See Labeling**

#### **7.13 Medical Officer Labeling Concerns**

Ifosfamide is rarely utilized as a single agent and is commonly used in higher doses than those utilized in the submitted study. The labeling should clearly indicate that the safety and efficacy of mesna tablets has not been established for doses of mesna higher than  $\sim 2.0$  g/m<sup>2</sup>.

The Indication and Usage as defined in the Product Draft labeling-

\_\_\_\_\_ would not be adequate for mesna tablets. The labeling should specifically refer to the combined use of iv and po mesna. The phrase \_\_\_\_\_ should replace the stated indication.

The sponsor should make it clear under adverse reactions that there is an increase in nausea and vomiting associated with combined iv and po mesna. The incidence of acidosis was significant in study 3126. This adverse event incidence (8/16 patients) should be reflected in the Product Labeling. As reported in the PDR in one study in which ifosfamide was given in doses of 2-2.5 g/m<sup>2</sup> metabolic acidosis were reported in 31% of subjects.

### **8 Dosing, Regimens and Administration Issues**

The selected doses of mesna for the iv/iv/iv and iv/po/po regimens were equally effective in preventing ifosfamide induced urotoxicity. As reported by Biopharmaceutics, higher exposures (AUCs) were noted for the iv/po/po regimen compared to the iv/iv/iv regimen and in addition accumulation in the iv/po/po arm was evident. It was not clear that such higher levels were necessary for urotoxic protection. This would be particularly true in light of the circumstance that higher plasma levels of mesna were associated with higher incidences of nausea and



## 10 Conclusions and Recommendations

### 10.1 Safety and Efficacy

The sponsor has demonstrated acceptable PK equivalency for the iv/po/po and iv/iv/iv regimens of mesna. Oral mesna appears to be safe and effective for utilization with ifosfamide to prevent ifosfamide-induced urotoxicity. Oral mesna appears to be associated with more nausea and vomiting than the iv preparation. The nausea and vomiting associated with oral mesna appears related pharmacokinetically to higher AUCs as well as to some degree of plasma accumulation. The higher dose of oral mesna above that of iv mesna counteracts possible deficits in bioavailability. This provides some assurance for efficacy in the event mesna is not absorbed adequately. The oral regimen has the advantage that patients may continue their oral mesna urinary prophylaxis as an outpatient.

It remains unclear whether the current dose ratios of mesna and ifosfamide will be appropriate for higher or lower doses of ifosfamide. The submitted studies failed to attain statistical significance, so the decision for approval is based on clinical evaluations. It should be noted that MD504 did reach statistically significant equivalence (1998 submission).

As the incidence of significant hematuria was similar in the po and iv only arms, as the adverse effects but for nausea and vomiting were similar ( a reasonable trade off of risk and benefit), and as there were no deaths reported in the study the agent would appear to be safe and effective as reported in study 3126.

The weight of evidence supports the likelihood that mesna does not (even in the face of higher plasma AUCs) protect against tumors and does not interfere with active ifosfamide metabolites.

Of concern is the lack of knowledge regarding (1) optimal mesna/ifosfamide ratios for higher doses of ifosfamide with respect to safety and efficacy; and (3) lack of adequate and well controlled studies supporting the wide spread off label use of ifosfamide in different doses and administration schedules. Patients must be well advised to maintain hydration on the po regimen. Additional post-marketing studies should be performed to answer the above questions and to provide data regarding special populations.

### 10.2 Recommendation on Approvability

Mesna tablets may be approved for the following indication--Mesna tablets are indicated for use in combination with iv mesna for the prophylaxis of ifosfamide-induced hemorrhagic cystitis in patients who have no contraindications to oral dosing and who would be expected to be able to maintain hydration during their course of chemotherapy.

**10.3 Labeling**

See Product Label

**/S/**

Gerald H. Sokol MD, MS, FCP  
Medical Office

**This is a representation of an electronic record that was signed electronically and  
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