3-18-98

NDA # 20-855
Mesnex[R] (mesna) Tablets

Sponsor: ASTA Medica, Inc.

Table of Contents

Table of Tables

I. General Information

a. Name of drug
   (1) Generic- Mesna
   (2) Trade- Mesnex^R
   (3) Chemical- Sodium-2-mercaptoethane sulfate, HS-CH2-CH2-SO3-Na
b. Pharmacologic category- chemoprotector
c. Proposed indication- as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis
d. Dosage form- 400 mg tablet for po administration
e. Related drugs- none
f. NDA Submission Date: March 25, 1997
   (1) Clinical Data: volumes 27-57 and 58-73
   (2) Case Report Forms (for patients who died or who discontinued drug treatment for toxicity): volumes 74-82
g. Minor Amendment Submission Date: December 17, 1997
   (1) CMC and Clinical Data: volumes 1-2

II. Manufacturing Controls

See Chemistry review for this application and for NDA #19-884.

III. Pharmacology

(Refer to Pharmacology Review for this application, and to the Medical and Pharmacology reviews for NDA #19-884).

IV. Clinical Background

A. Previous Human Experience with IV Mesna

NDA #19-884, Mesnex^R (mesna) Injection, was approved for the prevention of ifosfamide-induced hemorrhagic cystitis. The studies on which that approval was based are replicated as provided by the sponsor in Table 1 below.

To prevent the necessity for prolonged hospitalization, an oral formulation was developed, however it had the disadvantage of adverse taste. A 300 mg [redacted] film-coated tablet was developed and studied in Phase I and II trials (see IND #[redacted]. That formulation was however abandoned because dissolution decreased on long term storage. Later, a 400 mg film-coated tablet [redacted] provided a stable formulation resistant to change in dissolution rate on storage. It is this preparation that the sponsor plans to market in the US. Therefore, studies presented in this NDA which evaluated the [redacted] film-coated tablet are of greatest importance.

Table 1. Background/Overview of Clinical Investigations

Study	N	No. of Patients (%) with hematuria > 50 RBCs/hpf	
		Without mesna	*With mesna*
Morgan	44	7 (16%)	
Costanzi	43	11 (26%)	
Scheef/Klein	8		0 (0%)
	7	7 (100%)	
Osaka	46		3 (6%)
	46	14 (31%)	
Einhorn I	21		0 (0%)
	38	7 (18%)	
Einhorn II	32		0 (0%)
Antman	109		1 (0.9%)
	3	3 (100%)	
Havemann I	196		12 (6%)
Havemann II	56		2 (4%)
EORTC	68		4 (6%)
Sum		**16 - 100%**	**< 7%**

B. Comparison of the Pharmacokinetics of IV and Oral Mesna

Oral administration of a mesna solution or oral intake of Mesnex^{R} Injection has been approved in Canada, Great Britain, and Germany, and Mesnex^{R} Tablets have recently been approved in Germany, Great Britain, the Netherlands, Italy, and Denmark for the prevention of ifosfamide-induced hemorrhagic cystitis. The following background studies are reviewed as presented by the sponsor.

1. D-07093-0007(7)

Drinking Ampoules vs Film-Coated Tablets in Healthy Volunteers

This was a cross-over study conducted to compare the total urinary excretion rates of free thiols and reduced disulfides between mesna drinking ampoules and mesna [redacted] film-coated tablets. Six male volunteers were randomized to groups that received either 2 gm of mesna as drinking ampoules or 1.5 gm (5 300 mg tablets) of mesna. After a washout period of one week the alternative treatment was given. On the days of administration, urine samples were collected before and at 0-1, 1-2, 2-4, 4-8, and 8-24 hours after administration.

Mesna was generally well tolerated. Adverse effects included flu-like symptoms in this group of healthy volunteers. 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. Respectively in the drinking ampoule and film-coated tablet groups, the free thiols were 27.2 and 28.5, the reduced sulfides 58.1 and 68.8 and the total excretion 85.3 (77.9-91.7) and 90.3 (85.5-98.2).

2. D-07093-0008

Single Dose Safety, Tolerance and Pharmacokinetics 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. [redacted] tablets were given to normal healthy male volunteers. In this study single oral doses of 600, 1200, and 2400 mg as well as single iv doses of 600 mg of mesna were given to each of 10 volunteers with a 5-7 day washout period between dosing. Blood samples were collected at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 24 hours after po dosing, and 10, 20, and 30 minutes and 1, 2, 3, 4, and 8 hours after iv dosing to determine mesna and dimesna plasma levels. Urine was collected and pooled at hourly intervals for the first 8 hours and then from hours 8-10, 10-12,12-14, and 14-24. Twelve patients started the study but 2 dropped out secondary to adverse events after the third dosing interval but were replaced by two additional subjects.

Headache was the most frequent adverse drug event (ADE) followed by nausea (on four occasions accompanied by vomiting). Three subjects reported moderate headache, nausea, vomiting, and general aches and flushing. Two subjects complaining of sore throat, fever and general aches were felt to have viral syndromes. The tablets were well absorbed. The absorption and excretion of oral tablets was rapid, with a plasma t_{max} of less than 3 hours post-dosing and detectable urine excretion occurring only within the first hour. The mean total plasma bioavailability (plasma AUC oral/plasma AUC iv) of the 600 mg oral dose was 77.8 % for free mesna and 95.2% for dimesna, resulting in a mean absolute total thiol plasma bioavailability of 87.8% for the po formulation. For po mesna, the AUC values of the 600-2400 mg doses increased in a linear fashion with ratios of 1:2.7:8.5 for free plasma mesna, and ratios of 1:2.6:7.2 for dimesna.

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, which is the most important parameter for clinical practice, was 67.3% of that for the 600mg iv dose over the 24 hour period and 48.2% for the first 4 hours. The mean urinary recovery ratios for total thiols were 1:1.9:3.8 for the 600 mg/1200/2400 mg doses. The oral doses of 600 mg, 1200 mg and 2400 mg demonstrated close dose-linearity for the total excretion of mesna and dimesna with the ratio of total mesna plus dimesna of 1:1.9:3.8. This data indicates that a large proportion of the administered mesna is oxidized to dimesna in the blood and approximately equal portions of mesna and dimesna are excreted in the urine.

3. D-07093-0010

Multiple Dose Safety, Tolerance and Pharmacokinetic Study

This was a randomized four way cross-over Phase 1 study in 18 (16 evaluable) healthy male volunteers to confirm the results of the single dose trial and to determine whether further mesna dose schedules could be derived from the results of the single dose trial. The conventional iv schedule (600 mg three times daily at 0, 4, and 8 hours after ifosfamide) was compared to 2400 mg of mesna [redacted] film-coated tablets (300mg) once daily given at -1 hr, 1200 mg twice daily given at -1 hour and 4 hours, and a combination of iv and oral mesna

(600 mg given iv and 1200 mg given po once daily at 0 hours). There was a 5-7 day interval between treatments.

Skin reactions (rash, erythema, pruritis, flushing) were the most common ADEs reported. These were followed by gastro-intestinal symptoms including nausea, abdominal colic, diarrhea and flatulence. Two of 18 subjects dropped out due to ADEs. In an additional 3, dosing was interrupted. One patient developed bronchospasm during the second dosing period and responded to bronchodilators with improvement. Retreatment was associated with urticaria. In all, 3 patients suffered rash, pyrexia, lethargy, headache, and nausea.

With respect to PK, the excretion of mesna, dimesna and consequently total thiols was slightly higher on day 5 than on day 1 of the oral regimens. No accumulation in the plasma due to multiple dosing over five consecutive days was observed in the study.

Reviewer comment: It was during this study that it was discovered that on long term storage the [redacted] film-coated tablets [redacted] resulting in decreased dissolution. The [redacted] film coating was developed to eliminate that handicap. [redacted] tablets were used in the remaining studies as 400 and 600 mg tablets. The composition of these tablets compared to the [redacted] tablets is provided in the chemistry review. All the other studies to be reviewed utilize the [redacted] tablets except for D-07093-0019.

4. D-07093-0017

Single Dose Bioavailability Study of Mesna 400 mg Tablets

This study was a single dose bioavailability study performed in 25 subjects (1 dropout) with the objective of determining the absolute bioavailability of 400 mg [redacted] film-coated tablets with an iv injection of mesna. In addition, the relative bioavailability of 400 mg [redacted] film-coated tablets, 300 mg [redacted] film-coated mesna tablets, 600 mg [redacted] mesna tablets and mesna as an oral solution was evaluated. The study was a 5-way cross-over bioavailability study in healthy volunteers. The 5 treatment arms consisted of 1200 mg single oral dose as 3 400 mg [redacted] tablets, 1200 mg single oral dose as 4 300 mg [redacted] tablets, 1200 mg single oral dose as 2 600 mg [redacted] 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 for PK was obtained at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours for the first 4 arms and at 5, 10, 20, 30, 60 minutes, and 2, 3, 4, 6, 8, and 12 hours for the fifth treatment arm. Urine was collected pre-treatment and at appropriate intervals for PK evaluation.

Safety analysis indicated one subject withdrew secondary to loose stools, nausea, abdominal pain, rectal burning, vomiting and inability to eat. Adverse events replicated those reported in previous studies including rash, nausea, diarrhea, headache and dizziness.

Plasma PK evaluation indicated that the AUCs did not differ significantly between the four groups administered as oral formulations of 1200 mg (see Table 2 below as replicated from the sponsor). The oral AUCs were approximately twice those observed after iv administration of a 600 mg dose. The ratios of $AUC_{(0-1)}/AUC_{(inf)}$ were greater than 0.9 for all treatments suggesting an adequate sampling schedule. The maximal C_{max} after po loading was not statistically different between treatments (p=0.230). After iv dosing, the C_{max} was generally observed at the first post-infusion blood draw and was much higher than the C_{max} of the oral treatments. After po dosing, the C_{max} was reached approximately 2.6

hours after dosing. Considering the absence of an increased rate of absorption when a solution of mesna is given po, one would conclude that the absorption of po mesna is rate-limited by the absorption site rather than rate-limited by the formulation.

Regarding plasma dimesna, the plasma levels of dimesna were lower than those of mesna at all time points and after all treatments. As with mesna, the levels of dimesna were similar in the different oral treatment groups. The AUCs observed after oral dosing (1200 mg) were more than twice those observed for the iv (600mg) treatment. The C_{max} after po administration occurred for all oral treatments at approximately the same time as observed for mesna (approx. 2.9 hours). Those observations suggest a close relation between mesna and dimesna levels in plasma. The elimination half-life of dimesna is faster than for mesna (dimesna: 1hr for po vs 0.6 hr for iv; mesna: ~ 5 hours for po vs 2.74 hours for iv).

Urinary excretion profiles of mesna mimicked the plasma concentration profiles of the corresponding route of administration. The R_{max} (maximal rate of excretion) of mesna after po dosing occurred at the same time as the plasma C_{max} (2.6 hours). R_{max} did not differ significantly between the oral treatments and was lower than for the iv treatments, as expected. See Table 3 below as replicated from the sponsor.

The cumulative urinary excretion (CUE_{0-36}) of mesna in mmol (equivalent to the AUC in plasma) was similar in the po treatment groups. When compared to iv dosing, all oral doses appeared to result in greater CUEs. Taking different doses into account, the recovery of mesna was found to be less than for iv (approximately 79% recovery of the iv for the 400 mg tablet). The lowest $C_{min\ 0-24}$ did not differ significantly between oral treatments, with a mean of approximately 105 uM. In contrast, the iv treatment did not leave residual concentrations in most subjects' urine after 12 hours (mean=2.7uM).

Assuming that the cumulative urinary excretion of mesna over 0-36 hours is representative of the urinary bioavailability of mesna treatment, the 400 mg tablets were comparable to the other oral treatments for mesna urinary bioavailability since the 90% confidence interval 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 R_{max}, apparently related to the plasma C_{max}, was also found to be comparable between oral dose forms.

Urinary excretion of dimesna was apparently lower than for mesna. The R_{max} after po administration was usually observed at approximately 2.9 hours, a few minutes after the R_{max} of mesna, reinforcing the correlation between the two entities. The iv treatment did not result in any measurable urinary levels of dimesna after 9 hours. The oral treatments resulted in low but measurable levels of dimesna in many subjects for at least 24 hours. The 90% confidence interval limits of the 400 mg tablet were all within 80-120% of the means of the other treatments for CUE and R_{max}.

Adding up the percent of the dose recovered as mesna and dimesna in the urine in each collection interval resulted in a total recovery of approximately 71% of the dose for the oral treatments and 74% for the iv administration over 36 hours (minimal amounts are excreted between 24 and 36 hours). Thus the oral vs iv ratio of urinary bioavailability of mesna equivalents up to 36 hours is approximately 96%. See Table 4 below as replicated from the sponsor.

Table 2. Summary of Plasma Pharmacokinetics After a Single Dose

n= 24	A oral 3 x 400 mg	B oral 4 x 300 mg	C oral 2 x 600 mg	D oral 1.2 g Inj. Sol.	E iv 600 mg
Mesna					
AUC (micromole -hr)	133.14	139.14	133.28	135.69	67.37
C_{max} (micromolar)	40.45	45.01	41.73	42.39	173.91
T_{max} *(hr)*	2.73	2.54	2.56	2.67	0.09
KEL (hr-1)	0.19	0.19	0.18	0.18	0.36
$T_{½}$ (hr)	4.89	4.70	4.96	5.56	2.74
Dimesna					
AUC (micromole-hr)	49.29	53.24	50.57	49.70	23.53
C_{max} (micromolar)	17.01	19.15	18.05	17.71	26.45
T_{max} *(hr)*	2.92	2.81	2.92	2.90	0.17
KEL (hr-1)	0.76	0.77	0.74	0.67	1.27
$T_{½}$ (hr)	1.03	0.98	1.11	1.23	0.60

Table 3. Summary of Urinary Pharmacokinetics After a Single Dose

n= 24	A oral 3 x 400 mg	B oral 4 x 300 mg	C oral 2 x 600 mg	D oral 1.2 g Inj. Sol.	E iv 600 mg
Mesna					
CUE 0-36 (mmol-hr)	2.28	2.43	2.34	2.25	1.45
CUE 0-36 (% dose)	31.22	33.18	32.04	30.76	39.56
R_{max} *(mmol/h)*	0.64	0.70	0.70	0.65	1.12
T_{max} *(hr)*	2.56	2.56	2.56	2.77	0.50
$C_{min0-24}$ *(uM)*	103.67	107.50	102.87	109.25	2.17
Dimesna					
CUE 0-36 (mmol-hr)	1.38	1.47	1.39	1.38	0.63
CUE 0-36 (% dose)	37.88	40.16	38.06	37.89	34.44
R_{max} *(mmol/h)*	0.35	0.38	0.36	0.36	0.43
T_{max} *(hr)*	2.85	2.81	2.81	3.04	0.54
$C_{min0-24}$ *(uM)*	36.96	38.17	37.83	30.96	0.0

Table 4. Summary of Urinary Excretion after Single Mesna Dosing

n= 24	iv 600 mg		PO 1.2 g Inj. Sol.		PO 4 x 300 mg [redacted]		PO 3 x 400 mg [redacted]		PO 2 x 600 mg [redacted]	
Mesna excretion		Ratio*		Ratio*		Ratio*		Ratio*		Ratio*
0-4 hours (% dose)	37.52	100.0	20.14	53.7	23.06	61.5	20.91	55.7	23.06	61.5
0-24 hours (% dose)	39.55	100.0	30.47	77.0	32.95	83.3	31.07	78.6	31.75	80.3
0-36 hours (% dose)	39.56	100.0	30.76	77.8	33.18	83.9	31.22	78.9	32.04	81.0
Dimesna excretion		Ratio*		Ratio*		Ratio*		Ratio*		Ratio*
0-4 hours (% dose)	33.66		22.12		25.16		22.34		22.95	
0-24 hours (% dose)	34.44		37.68		40.09		37.81		37.93	
0-36 hours (% dose)	34.44		37.89		40.16		37.88		38.06	
Total mesna & dimesna excretion		Ratio*		Ratio*		Ratio*		Ratio*		Ratio*
0-4 hours (% dose)	71.18	100.0	42.26	59.4	48.22	67.7	43.25	60.8	46.01	64.6
0-24 hours (% dose)	73.99	100.0	68.38	92.4	73.04	98.7	68.88	93.1	69.68	94.2
0-36 hours (% dose)	74.00	100.0	68.65	92.8	73.34	99.1	69.10	93.4	70.10	94.7

*Ratio: Ratio iv/po (in %)

Reviewer conclusion: It is concluded that when given at a dose of 1200 mg, the 400 mg and 600 mg [redacted] film-coated tablets are bioequivalent to the 300 mg [redacted] tablets, and to the iv solution given po. The [redacted] film-coating did not appear to modify the absorption kinetics of mesna.

5. D-07093-0015

Effect of Food on Urinary Pharmacokinetics Study

This was a Phase 1 open, single-center, randomized 4 way cross-over study consisting of 1200 mg mesna iv in the fasting state, 2 600 mg [redacted] film-coated tablets fasting, 2 600 mg [redacted] film-coated 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 were collected at predose and at intervals up to 24 hours post dosing. Four subjects were replaced due to adverse effects associated with headache, myalgia, arthralgia, pyrexia, shivering, and flushing. All of the subjects withdrawn and 2 others had a marked drop in lymphocyte counts 24 hours after dosing. During the last three dosing intervals there was a transient fall in the mean lymphocyte counts for all 17 subjects. When the 3 dropouts were analyzed they all

showed the same slight increase in lymphocyte count after the first occasion and this was followed by a clear decrease in the lymphocyte counts on the second occasion and an even more pronounced fall on the third occasion. The difference between the evaluable subjects and the dropouts was statistically significant on the third occasion. All changes in lymphocyte counts were transient and fully reversible. The observed effects occurred independently of the type of administration and the sequence of administration (analysis of variance).

Regarding other safety issues, there were no severe adverse events and most adverse events were mild in severity. Headache was the most common ADE reported in all treatment groups. Abdominal pain was reported in at least one patient in each group and was highest in incidence in the oral iv solution group. Skin rash was most frequently reported in the iv infusion group. The incidence of ADEs in this study population was higher than expected.

An evaluation of urinary PK indicated that the values of urinary recovery of mesna and dimesna were comparably low (sampling bias of subjects being low excreters?). See Table 5 as replicated below from the sponsor's submission. 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.

Table 5. Mean 24 Hour Urine Excretion of Mesna, Dimesna, and Total Thiols (2 x 600 mg [redacted] Film-coated Tablets)

n= 12	iv 1.2 g		PO 1.2 g fasted		PO 1.2 g fed		PO 1.2 g Inj. Sol.	
Mesna excretion		Ratio*		Ratio*		Ratio*		Ratio*
0-4 hours (% dose)	36.6	100.0	13.2	36.1	8.0	21.9	14.5	39.6
0-24 hours (% dose)	37.1	100.0	17.6	47.5	16.9	45.6	21.0	56.3
Dimesna excretion		Ratio*		Ratio*		Ratio*		Ratio*
0-4 hours (% dose)	28.7		12.0		7.4		12.0	
0-24 hours (% dose)	29.9		21.4		20.7		23.7	
Total mesna & dimesna excretion		Ratio*		Ratio*		Ratio*		Ratio*
0-4 hours (% dose)	65.3	100.0	25.1	38.4	15.4	23.6	26.5	41.0
0-24 hours (% dose)	67.0	100.0	39.1	58.4	37.6	56.5	44.4	66.3

*Ratio: Ratio iv/po (in %)

Reviewer conclusion: It would appear that food did not significantly affect the absorption of the [redacted] film-coated tablets. There were no significant differences in the absolute urinary

bioavailability of total thiols when the [redacted] tablet was administered under fasted or fed conditions.

C. *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 1st study, single doses of 20, 30 and 40 mg/kg were administered to groups of 2 healthy male volunteers. Bad taste, soft stools in five of the six volunteers without changes in EKG, urinalysis, clinical chemistries or hematology values were noted. In the second study, three repeated injections, four hours apart of 20 and 30 mg/kg were given to groups of 2 adults. Again, bad taste was reported along with a slight rise in blood pressure and soft stools in two of the subjects with no adverse effects on vital signs, EKGs, urinalysis, clinical chemistry or hematology parameters. In the 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 for 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 1 episode each of nausea, pallor, and cardiovascular collapse (not apparently related to the mesna).

As reported by the sponsor (Tables 6 and 7) the adverse event profile in phase 1 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.

Table 6. Adverse Events - Summary of Single Dose Treatments in Phase 1 Studies in Healthy Volunteers*

	600 mg po tablet		1200-1500 mg po tablet		2400 mg po tablet		1200 mg po iv solution		600 mg iv		1200 mg iv	
	N	%	N	%	N	%	N	%	N	%	N	%
N exposed	11	100	59	100	12	100	41	100	37	100	16	100
global incidence preferred term	5	45.5	24	40.7	7	58.3	11	26.8	8	21.6	13	81.3
headache	2	18.2	9	15.3	4	33.3	7	17.1	4	10.8	7	43.8
hypoaesthesia	1	9.1	0	0	0	0	0	0	0	0	0	0
malaise	1	9.1	0	0	1	8.3	0	0	1	2.7	0	0
myalgia	1	9.1	1	1.7	0	0	1	2.4	1	2.7	0	0
nausea	1	9.1	2	3.4	2	16.7	0	0	2	5.4	0	0
pharyngitis	1	9.1	2	3.4	0	0	1	2.4	0	0	0	0
somnolence	1	9.1	1	1.7	1	8.3	2	4.9	1	2.7	1	6.3
upper resp. infect	1	9.1	2	3.4	0	0	0	0	0	0	0	0
vomiting	1	9.1	1	1.7	2	16.7	0	0	1	2.7	0	0
dizziness	0	0	7	11.9	1	8.3	1	2.4	1	2.7	1	6.3
abdominal pain	0	0	3	5.1	1	8.3	3	7.3	0	0	1	6.3
coughing	0	0	3	5.1	0	0	0	0	0	0	0	0
diarrhea	0	0	3	5.1	0	0	1	2.4	0	0	1	6.3
anorexia	0	0	2	3.4	1	8.3	1	2.4	0	0	0	0
flushing	0	0	2	3.4	0	0	2	4.9	1	2.7	2	12.5
injection site reaction	0	0	2	3.4	0	0	0	0	0	0	2	12.5
back pain	0	0	1	1.7	0	0	3	7.3	0	0	1	6.3
dyspepsia	0	0	1	1.7	0	0	0	0	0	0	2	12.5
paraesthesia	0	0	1	1.7	1	8.3	0	0	0	0	1	6.3
renal pain	0	0	1	1.7	0	0	0	0	0	0	1	6.3
rigors	0	0	1	1.7	0	0	2	4.9	0	0	2	12.5
fatigue	0	0	0	0	1	8.3	0	0	0	0	0	0
conjunctivitis	0	0	0	0	0	0	3	7.3	1	2.7	1	6.3
arthralgia	0	0	0	0	0	0	2	4.9	0	0	2	12.5
application site reaction	0	0	0	0	0	0	0	0	1	2.7	5	31.3
photophobia	0	0	0	0	0	0	0	0	0	0	3	18.8
dehydration	0	0	0	0	0	0	0	0	0	0	1	6.3
dysuria	0	0	0	0	0	0	0	0	0	0	1	6.3
sweating increased	0	0	0	0	0	0	0	0	0	0	1	6.3

*Counts and incidences for those occurring at a rate of 5% or greater in studies D-07093-0007, D-07093-0008, D-07093-0015 and D-07093-0017

Table 7. Adverse Events - Summary of Single Dose Treatments in Phase 1 Studies in Healthy Volunteers by Body System*

	600 mg po tablet		1200-1500 mg po tablet		2400 mg po tablet		1200 mg po iv solution		600 mg iv		1200 mg iv	
	N	%	N	%	N	%	N	%	N	%	N	%
N exposed	11	100	59	100	12	100	41	100	37	100	16	100
global incidence	5	45.5	24	40.7	7	58.3	11	26.8	8	21.6	13	81.3
body system												
application site	0	0	2	3.4	0	0	0	0	2	5.4	7	43.8
autonom. Nervous	1	9.1	5	8.5	2	16.7	4	9.8	2	5.4	3	18.8
body as a whole	3	27.3	12	20.3	5	41.7	8	19.5	4	10.8	7	43.8
central and periph. nervous	3	27.3	16	27.1	6	50.0	8	19.5	4	10.8	8	50.0
gastrointestinal	1	9.1	7	11.9	3	25.0	6	14.6	2	5.4	4	25.0
liver and biliary	0	0	1	1.7	0	0	1	2.4	0	0	0	0
metabolic and nutritional	0	0	0	0	0	0	0	0	0	0	1	6.3
musculo-skeletal	1	9.1	2	3.4	0	0	4	9.8	1	2.7	2	12.5
psychiatric	2	18.2	4	6.8	2	16.7	3	7.3	1	2.7	1	6.3
resistance mechanism	1	9.1	5	8.5	0	0	1	2.4	0	0	0	0
respiratory	1	9.1	6	10.2	0	0	2	4.9	0	0	0	0
skin and appendages	0	0	3	5.1	0	0	3	7.3	0	0	1	6.3
urinary	0	0	1	1.7	0	0	0	0	0	0	2	12.5
vascular	0	0	2	3.4	0	0	2	4.9	1	2.7	2	12.5
vision	0	0	0	0	0	0	3	7.3	2	5.4	4	25.0

*Counts and incidences for those occurring at a rate of 5% or greater in studies D-07093-0007, D-07093-0008, D-07093-0015 and D-07093-0017

D. Literature References

The sponsor has provided a review of 75 pertinent literature references dealing with the utilization of po mesna (in various forms) in adequate as well inadequate protective doses in man in which mesna was administered as a means to attain uroprotection. A summary of the most important of these articles published between 1981 and 1996 is proved below in abbreviated tabular form.

Table 8. Literature References

Year	Journal	Author	Drugs Used (Dose)	Mesna Formulation	# Urotoxicity
1990	Cancer Chemo	Andersen	I 1.5g/m^{2}x8, VP16	iv, po low dose (200 po)	3/47
1983	Euro J Cancer	Araujo	I 2250 mg/m^{2}x4 + ?	840 mg po q4 x3	10/70 microhem
1991	J Surg Onc	Araujo	I 3 gm/m^2 x5 + Cisplatin	40% of I dose	2/21microhem
1993	Brit J Ca	Bleehan	VP16, I 5 gm/m^2 x1	po or iv	3/149 cystitis
1994	19th Cong Abst	Bordenave	I 2 g/m^2 x1,Cisplatin	po 1000 mg/m^2 x2	no urotoxicity
1995	Oncology	Brocato	I 2.5 g/m^2 x2, Epirubicin, Cisplatin	40% of I dose	gr1:56/1046, gr2: 24/1046
1990	Sem Onc	Cabanillas	I 1.33 g/m^2 x3, VP16	500 mg (sol)	no macrohem
1989	Brit J Ca	Cerny	I 2 g/m^2 x3, po VP16	400 mg at 0, 4, 8 hr	no urotoxicity
1991	J Ca Res Cl Onc	Cerny	I 1.75g/m^2 x5 infusion	400 mg po at 4, 8 hr	no urotoxicity
1990	Ca Chemo Pharm	Cervellino	I 3.5 g/m^2 x5 infusion	40% of I dose at 10, 12 hr	3/18 microhem
1991	Oncology	Cervellino	I 3.5 g/m^2 x5 infusion	40% of I dose at 10, 12 hr	3/28 microhem
1994	ASCO	Cervillino	I 3 g/m^2 x3, Epirubicin	40% of I dose	Urotoxicity < 2%
1995	Acta Onc	Cervellino	Cisplatin, I 2.5 g/m^2 x5	1000 mg/m^2 po x1	1/30 gr3 urotoxicity
1993	ASCO	Rohrbach-Klinik	I po?	po?	0/127 hematuria
1989	JNCI	Edmonson	I 2.5 g/m^2 x3, VP16	iv and po?	1/44 gross hematuria
1995	Sem Onc.	Elisson	I 1.4 g/m^2 x3, Dox, VCR,VP16	iv, po 1000 mg	18/36 micro;1/36 macro
1992	Ann Onc	Frustaci	I 1.8 x5, 2-2.5 x2, 3 g/m^2 x2	po (80%)	0/27 UTI symptoms
1993	Amer J Clin Onc	Gonzolez	Mito, I 5 g/m^2 x1, Cisplatin/Vin I/Cisplatin	1600 mg/m^2 po at 4, 8, 12 hr	15% gr1-2; 7.1% gr1-2
1990	ASCO	Goodman	I 1-1.5 g/m^2 x3	iv and po	0/6 hem cystitis
1992	ASCO	Goodman	I	iv and po (40%)	1/60 gross hematuria
1996	Sem Onc	Goren	I - various doses	iv and po (2 doses)	review of 47 studies and of 6475 courses
1993	Br J Can	Highley	po I 0.5 g bid x14d	po 60% of I dose bid	1/42 hematuria
1990	Amer J Cl Onc	Holoye	I 2 g/m^2 x5	po 400 mg at 4, 8 hr	20: 6-10 RBC; 3:11-50 RBC
1995	J Can Res Clin Oncol	Katz	I various doses	po at 8 hr, 2x I dose	1.4% microhem
1995	ASCO	Lemke	I 1 g/m^2 x3, Cisplatin	iv and po 400 mg/m^2 at 2, 6 hr	0/15 hem cystitis
1996	J Clin Onc	Leone	I 2 g/m^2 x3,Vinorelbine	iv and po 800 mg/m^2	6/45 gr1-2 cystitis
1994	J Clin Onc	Murad	Bleo, I 2 g/m^2 x3,Carbo	iv and po 40% of I dose at 8 hr	3/35 gr2; 6 gr1 hematuria

Year	Journal	Author	Drugs Used (Dose)	Mesna Formulation	# Urotoxicity
1984	Tumori	Nobile	I 1.8 g/m^2 x5	iv 360 or po 720 mg/m^2	po: 8/57 courses hematuria; iv: 6/72
1993	J Clin Onc	Perez	I 2 g/m^2 x3, Mitoxantrone	po 2000 mg at 8 hr	2/48 gr2; 4/48 gr1
1993	ASCO	Rabinovich	I 2 g/m^2 x3, Cisplatin	800 mg/m^2 at 8 hr	1/23 gr1 hematuria
1995	J Clin Onc	Rodriquez	MINE, ESHA I 4 g/m^2 over 4d	500 mg po, 4g iv	0 episodes hematuria
1986	Can Chem Pharm	Thatcher	I 5 g/m^2 x1	iv 5 g/m^2 + po 3 gm/m^2 x3 at 4, 8, 12 hours	4% mild cystitis
1990	Can Chem Pharm	Toma	Epirubicin, I 1.5 g/m^2 x5	40% of I dose, solely po	0/16 hematuria
1995	Cancer Invest	Turill	Carbo, I 1.5 g/m^2 x4	400 mg/m^2 qid po	8/25 microhematuria
1996	Amer J Clin Onc	Vallejo	I 2 g/m^2 x3,Vinorelbine	iv + 2000 mg po at 8 hr	2 gr1; 1 gr2 hematuria
1991	12 Int Conf Chem	Varini	I 1.2 g/m^2	none vs 500 mg/m^2 at 4, 8 hr	44% vs 17% microhem wo/w mesna
		Varini	I 1.8 g/m^2 x5	iv 360, then 720mg/m^2 po x2 vs 720 mg/m^2 po at 0, 4, 8 hr	iv/po: 17% microhem po: 18% macro + 18% micro
1995	Amer Soc Clin Onc	Vincent	I 250mg po	po 200 mg bid	5% mild to mod hematuria

I = Ifosfamide

Reviewer comment: These selected uncontrolled human studies utilizing various forms of oral mesna tablets (generally of an unstated formulation) or of 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 strong literature base for efficacy and safety in support of the approval of oral mesna as a uroprotector. Though most authors and the sponsor fail to specify the formulations used, other data presented in this NDA demonstrate the similarity of the various forms of mesna - iv solution, [redacted] tablets, and [redacted] tablets.

V. Clinical Studies

A. Controlled Studies

Tables 9 and 10, adapted from the sponsor's submission, summarize the three randomized studies. Table 9 summarizes the types of studies and design features, and Table 10 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.

Table 9. 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
				Controlled Clinical Studies				
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 10. Controlled Studies: Major Efficacy Outcomes

Study	Ifosfamide Dose	No. Pts randomized to each Mesna Sequence	No. of Dropouts in each Sequence	Major Efficacy Outcomes
		Controlled Clinical Studies		
D-07093-0018 Multicenter	1.2 - 2.0 g/m² 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/m² 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/m² 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 11 and 12 summarize respectively the same parameters for the uncontrolled studies. The first two controlled studies will be reviewed here, which will be followed by a review of three uncontrolled studies, including Study D-07093-0019.

Table 11. 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
				Uncontrolled Clinical Studies				
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 12. Uncontrolled Studies: Major Efficacy Outcomes

Study	Ifosfamide Dose	No. Pts randomized to each Mesna Sequence	No. of Dropouts in each Sequence	Major Efficacy Outcomes
		Uncontrolled Clinical Studies		
D-07093-0016 Multicenter	1.2 - 2.5 g/m²	iv/po/po: 188	18	No macrohematuria; 8/188 (4%) severe hematuria (> 50 RBCs/hpf)
MED700 Multicenter	1.2 - 2.0 g/m² daily over 3-5 days	po/po/po: 31	2	No macrohematuria or severe hematuria observed
MED200	1.5 g/m² daily over 5 days	iv/po/po: 11	3	No case of hematuria ≥ 5 RBCs/hpf

1. Study D-07093-0018

Open label, randomized, comparative 2-way cross-over multiple dose study of efficacy and safety of an IV and IV/oral regimen of mesna in patients treated with Ifosfamide

The Study Director was W. Brade, M.D. The other eight investigators and their locations are listed in Table 13 below. Out of a planned 120 patients, 66 patients were enrolled and randomized as of the NDA cutoff date. Therefore, this NDA contains an interim report of this study, with data collected at six study sites in the US, and PK data collected at three centers in 11 patients during the mesna iv+po cycle.

Table 13. Study D-07093-0018: Investigators and Locations

Center	Investigator	Location
1*	L. Anthony	Vanderbilt University Medical Center, Nashville, TN
2*	A. Chang	The Genesee Hospital, University of Rochester, Rochester, NY
3*	M. Castro	Glens Falls Cancer Center, Glens Falls, NY
4	T. Thigpen	University of Mississippi Medical Center, Jackson, MS
5*	C. Rosenthal	Long Island College Hospital, Brooklyn, NY
6*	T. Goodman	Ellis Hospital, Schenectady, NY
7*	G. Elfenbein	H. Lee Moffett Cancer Center, Tampa, FL
8	A. Lipton	Hershey Medical Center, Hershey, PA

*Center had enrolled at least one patient as of December 1996

a) Objectives

The objectives of the protocol are to compare the clinical efficacy of the two regimens, mesna iv and mesna iv+po, in the prevention of ifosfamide-induced severe hematuria (defined as >50 RBCs/hpf or visible blood in the urine), to compare the safety and tolerability of the two regimens, and as amended, to permit collection of comparative pharmacokinetic data for mesna and dimesna in urine at selected centers. (The selection process for determining which centers would be utilized was not stated.)

b) Rationale

The rationale of the study is that mesna has been approved in iv form in the US for use as a detoxifying agent against the urotoxic metabolites of ifosfamide resulting in a lower incidence of hemorrhagic cystitis than that seen when ifosfamide is used alone. PK studies have been done in human volunteers after iv and po administration and in patients after regimens of iv or oral mesna only, or of iv plus po. Studies reviewed previously indicated that the urinary availability of po mesna was approximately 48 - 79% of the iv preparation. Three different oral mesna formulations (the 400 mg and 600 [redacted] film-coated tablets, the 300 mg [redacted] film-coated tablets, and the iv solution given po) were all found to be bioequivalent to each other. The urinary excretion of mesna and dimesna after po dosing was nearly identical for the different

oral dosage forms. A regimen comprised of an iv mesna dose followed by an oral dose at 2 hours and at 6-8 hours was reasonably tolerated and therefore, chosen for further evaluation in this study.

c) Experimental Design

The experimental design of the study was a Phase 3, multicenter, randomized, active controlled, cross-over trial designed to assess the efficacy and safety of a combined iv+po regimen of mesna vs an iv regimen of mesna in cancer patients treated with ifosfamide.

The experimental arm consisted of an iv mesna dose at 0 hours, followed by oral doses of mesna at 2 hours and at 6 hours. The iv mesna dose was to be 20% of the ifosfamide dose, whereas, the oral doses were to be 40% of the ifosfamide dose. The control group would receive iv mesna equal to 20% of the ifosfamide dose at 0, 4,and 8 hours - the currently approved dosing regimen in the US. Urine PK measurements were obtained in some patients (selection criteria not stated as to how PK patients were selected). The inclusion criteria and treatment plan are given below.

Table 14. Main Criteria for Inclusion

- Scheduled to receive at least two cycles of chemotherapy containing ifosfamide with a daily dose of 1.2 - 2.0 g/m^2 given on 3-5 consecutive days as iv infusion over 30-60 minutes, with a total dose of at least 4.5 g/m^2 per cycle. The time interval between the cycles had to be in the range of 3-6 weeks. The ifosfamide regimens in the two study cycles had to be identical.
- Age $\geq$ 18 years
- ECOG performance status $\leq$ 2
- Informed consent
- No history or current findings of conditions associated with an increased risk of hematuria
- No concomitant treatments associated with an increased risk of hematuria

Table 15. Treatment Plan

Treatment Arm (Dose Regimen)	Mesna dose in % of ifosfamide dose				
	0 h	2 h	4 h	6 h	8 h
iv	20% iv		20% iv		20% iv
iv+po	20% iv	40% po		40% po	

Patients were randomized to either the iv or iv+po mesna regimen for 1 cycle, then crossed over to the alternative mesna regimen in cycle 2.

d) Study Endpoints

The study endpoints consisted of the incidence of severe hematuria, and safety and tolerability. Hematuria was assessed by counting RBCs/hpf and examining the urine for visible blood. On days 1-5, a midstream urine sample was taken 2 hours prior to the first mesna dose of each day of the cycle. The samples were analyzed at the study sites. On days 6-10, the patients performed a test strip for hematuria every morning and maintained a patient diary. In the circumstance that the test strip appeared positive to the patient, the result was to be confirmed by a microscopic urinalysis using the RBCs/hpf method. Only the results of the urinalysis was to be used for the statistical evaluation.

The endpoint of safety and tolerability was assessed by observing and evaluating vital signs, laboratory tests and adverse events.

Statistical Consultation: The results of the FDA statistical analysis and consultation are described below. See Dr. Gang Chen's Statistical Review for additional details.

As provided by the sponsor, the statistical evaluation of the study endpoints was performed by comparing the iv+po vs the iv schedule according to the following levels: 0-20 RBCs /hpf = Level I, 21-50 RBCs/hpf = Level II, >50 RBCs/hpf = Level III, and visible blood = Level IV. The target parameter was the rate of severe hematuria (defined as Levels III and IV).

Carryover effects (treatment by period interactions) were investigated. If the hypothesis of no carryover effects cannot be rejected (alpha=0.10), the occurrence of severe hematuria was compared intra-individually disregarding the sequence of treatment. Otherwise, the data obtained in the first cycle was compared inter-individually.

An upper bound for the 95% confidence limit was estimated on a normal approximation for the absolute difference d = p1-p2 where p1 is the probability of observing severe hematuria in the iv+po schedule, and p2 is the respective probability for the iv schedule. The two schedules were considered equivalent if the upper bound of the 95% confidence limit was ≤ 0.10. The analysis was performed for patients evaluable for hematuria according to protocol. Additionally, an intent-to-treat analysis was presented taking into account all randomized patients. Missing data was submitted by last value carrying forward principles.

The internal validation of the iv schedule vs placebo (i.e., historical control) consisted of a comparison to a group of 45 Japanese patients who received a five day schedule of 2 gm/m^2/day ifosfamide and placebo in a randomized controlled study with a parallel group design. Comparisons were made between this historical control group and the patients of the current study who received the same ifosfamide schedule. The two groups were described in detail by demographic, anamnestic and therapeutic data. The rate of severe hematuria observed with the standard iv schedule in the current study (patients receiving 2 gm/m^2/day ifosfamide) were compared to the respective rate observed in the placebo group of the Japanese trial by means of descriptive statistics.

Safety and tolerability were assessed in all patients who received mesna at least once. Incidences of ADEs were computed according to WHO terminology. Vital and laboratory parameters were screened for individually remarkable changes and analyzed for trends.

e) Study Results

(1) Demographics, Protocol Deviations

At the time of the original NDA submission, a total of 66 patients had been recruited and randomized to treatment with either a sequence of mesna iv+po/iv (N=33) or with the sequence of mesna iv/iv+po (N=33). All patients randomized received at least one dose of mesna. Of those, 17 patients were discontinued prematurely for reasons summarized below.

Table 16. Patients Discontinued Prematurely and Reason(s) for Discontinuation

Center/ Patient No.	Last Administration of Mesna (Cycle/Day)	Reason
Treatment Sequence: iv+po/iv		
1/5	1/5	Hospitalization for neutropenia
2/5	1/2	Neurotoxicity
3/7	1/5	Hematuria, death
3/10	1/5	Progression of disease
3/12	2/5	Death
5/3	1/5	Death
5/8	1/3	Death
5/12	1/2	Sepsis, death
6/2	1/5	Lost to follow-up
Treatment Sequence: iv/iv+po		
1/7	1/3	Upper respiratory infection and hepatotoxicity
3/15	1/5	Thrombocytopenia due to chemotherapy
3/16	1/5	Insertion of foley catheter
5/1	1/5	Psychosis
5/2	2/4	Withdrew consent
5/10	1/3	Withdrew consent
5/11	1/3	Leukopenia, aphasia, thrombocytopenia
6/11	2/5	Lost to follow-up

All 66 patients entered in the study were included in the intent-to-treat analysis. A total of 27 patients (13 on mesna iv+po/iv; and 14 on mesna iv/iv+po) were excluded from the per-protocol analysis (17 discontinued prematurely as noted above and 10 more for protocol violations or missing data) and were included only in the intent-to-treat analysis. Thus, a total of 20 patients in the mesna iv/po/iv sequence and 19 patients in the mesna iv/iv/po sequence were included in the per-protocol analysis.

As reported by the sponsor, the baseline demographic characteristics of patients included in the intent-to-treat analysis indicated that patients appeared to be balanced reasonably for sex, race, age weight, and ECOG performance status.

Reviewer comment: It is not clear that the sponsor has addressed the adequacy of balancing across groups in the per-protocol analysis.

Baseline disease status was reasonably balanced in that most patients entered had lung cancer with a time from first diagnosis of tumor of 8 months for patients in the iv+po/iv sequence (range 0-78 mos) and 10 months for the patients in the iv/iv+po sequence (range-0-211 mos). Of the 66 patients enrolled, 64 had received previous treatment for their tumors: 48 having undergone chemotherapy, 15 (7 in the iv+po/iv sequence and 8 in the iv/iv+po sequence) with ifosfamide.

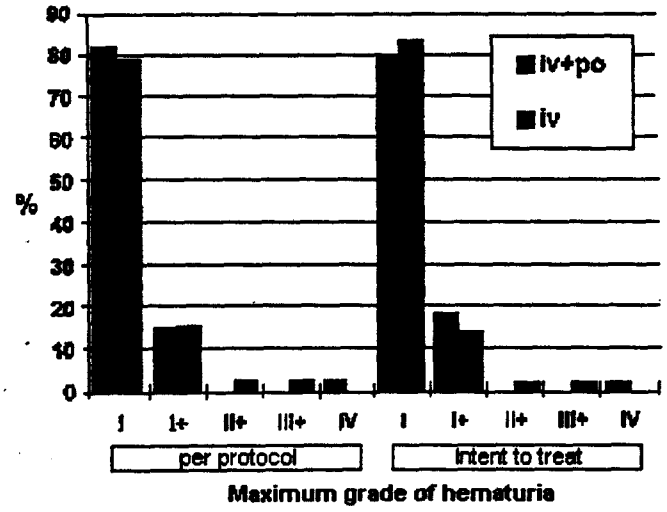
On study, 54.5% or 36/66 patients received a dose of ifosfamide of 1.2 gm/m^2 over 5 days, while the total ifosfamide dose ranged from 2.6-10 gm/m^2. Patients who received a total dose of ifosfamide <4.5 gm/m^2 per cycle were excluded from the per-protocol analysis (2 patients in the iv+po/iv sequence and 4 patients in the iv/iv+po sequence).

Hydration and concomitant medications appeared to be reasonably matched in the study between the two groups. There were no major differences between mesna regimens with respect to frequency of use of any of the ATC classes of concomitant medications.

(2) Efficacy Results: Hematuria

The distribution of hematuria grades, the primary endpoint of this study, as provided by the sponsor in the per-protocol and intent-to-treat populations is shown below. As demonstrated in the figure, the two mesna regimens appeared to be equally uroprotective.

Figure 1. Maximum grade of hematuria



The statistical comparison as provided by the sponsor is replicated below.

Table 17. Comparison of the Incidence of Grade III or IV Hematuria* Observed with Mesna iv+po and Mesna iv Regimens - Intent-to-Treat and Per-Protocol Populations

Analysis	Incidence of Grade III or IV Hematuria		Difference	95% confidence bound
	iv+po	iv		
intent-to-treat	1/60 (1.7%)	1/58 (1.7%)	n/a	n/a
per-protocol	1/39 (2.6%)	1/39 (2.6%)	0.0%	6.0%

Key: Grade I = 0-20 RBCs/hpf; Grade II = 21-50 RBCs/hpf; Grade III = > 50 RBCs/hpf; Grade IV = visible blood

The results of the statistical analysis as performed by the sponsor indicate that there was no difference between the iv+po regimen and the approved iv regimen with respect to the incidence of Grades III or IV hematuria.

Two patients had Grade III or IV hematuria during the study, one during the iv+po cycle (this patient had a bladder tumor and was ineligible for the evaluation of hematuria) and one during the iv cycle (see below).

Table 18. Patients with Grade III or IV Hematuria - Intent-to-Treat Population

Patient	Sex/Age	Treatment Sequence	Ifos Regimen	Hematuria iv+po cycle			Hematuria iv cycle		
				Grade*	Day	Duration	Grade*	Day	Duration
3/7*	m/68	iv+po/iv	1.2 g/m² x 5 days	IV	6	> 19 days	-	-	-
6/8	m/71	iv+po/iv	1.2 g/m² x 5 days	I	-	-	III	8	1 day

*Patient 3/7 had Grade IV hematuria for 2 days, then alternated between Grade II and III

In addition, three patients (for a total of 5) had Grade II or Grade III hematuria after completing the 1st cycle (>10 days after the start of ifosfamide treatment). Two of these had hematuria after treatment with the mesna iv regimen (see below).

Table 19. Incidence of Grade II or III Hematuria - Intent-to-Treat Population

Patient	Cycle/day	Schedule	Hematuria grade
2/2	1/24	iv+po	II
3/9	1/12	iv	II
5/1	1/23	iv	III

(3) Safety Evaluation

The overall incidence of ADEs and adverse drug reactions (ADRs) was recorded utilizing WHO coding criteria. ADRs exclude those signs or symptoms whose relationship to mesna is considered by the investigator to be unlikely or nonexistent, or which existed before the start of treatment with mesna, and did not increase in intensity

which existed before the start of treatment with mesna, and did not increase in intensity during treatment. Among 58 patients who received the iv mesna regimen, 57 (98.3%) sustained ADEs and 11 (19%) sustained ADRs; among 60 patients who received the iv+po regimen, 59 (98.3%) sustained ADEs and 13 (21.7%) sustained ADRs.

It is apparent that nausea and vomiting were the two most common ADEs. They generally appeared to be equal in incidence across regimens: 33 incidents of nausea in the iv arm vs 30 in the iv+po arm, and 20 incidents of vomiting in the iv arm vs 22 in the iv+po arm. All other ADEs appeared to be relatively similar in the two groups.

The incidence of adverse events occurring in 5% or more of patients is recorded below.

Table 20. Listing of Serious Adverse Events Safety Population

Patient	Mesna Regimen	Serious Adverse Event (Preferred Term)
1/2	iv+po	Fever, Granulocytopenia
1/5	iv+po	Granulocytopenia
1/6	iv	Eye infection
2/2	iv	Thrombocytopenia
	iv+po	Thrombocytopenia
3/2	iv	Myeloproliferative disorder
	iv+po	Myeloproliferative disorder
3/3	iv	Fever, granulocytopenia, nausea, sepsis, vomiting
3/6	iv	Gastric ulcer hemorrhagic, leukopenia, thrombocytopenia
3/7	iv+po	Angina pectoris, fibrillation atrial, hemorrhage NOS, leukopenia, pneumonia, thrombocytopenia
3/8	iv	Anorexia, dizziness, leukopenia
3/9	iv+po	Abdominal pain
3/10	iv+po	Dehydration, granulocytopenia, vomiting
3/12	iv	Acidosis, fibrillation atrial, leukopenia, renal function abnormal, sepsis, syncope, tachycardia ventricular, thrombocytopenia
3/13	iv+po	Dehydration, leukopenia, thrombocytopenia
3/14	iv	Dehydration, leukopenia, thrombocytopenia, vomiting
	iv+po	Dehydration, vomiting
3/15	iv	Thrombocytopenia
3/16	iv	Anemia, leukopenia
5/1	iv	Sepsis
5/3	iv+po	Death
5/8	iv+po	Granulocytopenia
5/9	iv	Anemia, granulocytopenia, syncope
5/10	iv	Leukopenia, thrombocytopenia
5/11	iv	Dysphagia, leukopenia, thrombocytopenia
5/12	iv+po	Anemia, granulocytopenia, sepsis, thrombocytopenia, urinary tract infection
6/3	iv+po	Anemia Granulocytopenia
6/5	iv	Fever, infection bacterial
6/6	iv	Infection bacterial
6/16	iv	Confusion
7/1	iv	Fever

Laboratory tests were graded using SWOG criteria. With respect to the incidence of thrombocytopenia, this was observed in the iv and iv+po mesna regimens in 13 and 14 patients, respectively. The incidence of granulocytopenia was 9 in the iv arm vs 12 in the iv+po arm, while the incidence of leukopenia was 12 in the iv arm and 7 in the iv+po arm. In patients treated with combination chemotherapy or with ifosfamide chemotherapy alone, the distribution of maximum grades of leukopenia by SWOG criteria was not influenced by the mesna regimen used. There was a trend for leukocytes to remain depressed in the iv+po arm at 9-16 days.

There were no trends indicating clinically significant differences in albumin, BUN, cholesterol, electrolytes, liver function tests, or in urinalysis results between the two mesna regimens.

The incidence of death was significantly higher in the iv+po arm, with 5 patient deaths vs 1 in the iv arm. This difference attained statistical significance. As demonstrated in Table 20 above, there were 13 serious ADEs during treatment with the iv+po regimen vs 18 in the iv regimen. There appeared to be no significant differences between the mesna regimens with respect to systolic or diastolic blood pressure, pulse or temperature. ECOG performance status appeared to deteriorate similarly in both groups.

(4) Conclusions

(a) Sponsor

The primary efficacy parameter was the occurrence of severe microhematuria defined as >50 RBCs/hpf (grade III hematuria) and macrohematuria or visible blood (grade IV hematuria). Grades III and IV hematuria occurred in only one patient in each group.

In the sponsor's intent-to-treat analysis, in the iv+po treatment sequence 1/60 (1.7%) of patients sustained a Grade III or IV hematuria, and by the per-protocol analysis 1/39 (2.6%) sustained Grade III or IV toxicity. In the iv sequence, 1/58 (1.7%) of patients sustained Grade III or IV hematuria in the intent-to-treat analysis and 1/39 (2.6%) in the per protocol analysis. The difference between the regimens in the per-protocol analysis was 0.0% with an upper bound for the 95% confidence interval of 6%.

Thus, the sponsor's intent-to-treat analysis of the primary parameter revealed equivalent uroprotection with the proposed mesna iv+po and the approved mesna iv regimen.

Due to missing data on 12 patients enrolled in Center 5, the sponsor performed an additional analysis that excluded these patients. In this analysis, 1/48 (2%) in the iv+po arm and 1/46 (2%) in the iv only arm had Grade III or IV hematuria. The difference was 0% and upper bound for the 95% confidence was again 6%. Thus, exclusion of the data from Center 5 had no bearing on the sponsor's overall results.

At the FDA's request, the sponsor submitted an amended report (Vol. B2) in February 1998 updating the efficacy analysis with the addition of 5 new patients that had been accrued since the original NDA submission (4 in the iv/iv+po arm

and 1 in the iv+po/iv arm from Center 5). In this submission, the sponsor re-analyzed the data for the primary efficacy parameter for a total of 71 patients, **including the 12 patients from Center 5.** The sponsor's result indicated that the upper bound for the 95% confidence limit was 10.5%, slightly above the equivalence range specified in the protocol.

With respect to tolerability, the sponsor noted that the most frequently occurring ADEs were gastro-intestinal in nature. The frequency of nausea and vomiting was similar in the two groups. The incidence of grade 3 or 4 leukopenia was also comparable in the two groups. The sponsor maintained that none of the 6 deaths in the study were related to the study drugs.

(b) FDA

In the intent-to-treat analysis, the sponsor counted all patients who dropped from the study as successes. This was felt by the FDA statistician to be problematic, as the loss of subjects complicated analysis and interpretation. With an approximate loss of 41% of patients (27/66 patients, 13 on iv+po/iv; and 14 on iv/iv+po) in the study, any analysis based on the cross-over data may not be valid. As most patients completed the first cycle of the study, the FDA statistician performed a re-analysis based on the first cycle data only (using parallel comparison). This re-analysis included all patients who had records in the first cycle of the study. 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 1/33 (3%) in the iv group, with a 0% difference and an upper bound for the 95% confidence limit (one-sided) of 9.9%. This suggested that the two treatment regimens were statistically equivalent.

During a June 1997 FDA audit of one of the study sites (Center 5, C. Julian Rosenthal, MD), it was learned that for many of the patients adequate records of the conduct of the required urinalysis measurements were not kept. In addition, concomitant medications and adverse events were not always accurately recorded. In some patients, data were included for non-study cycles of chemotherapy and not recorded for study related cycles. These findings have been acknowledged in writing by the sponsor in its December submission. The Agency contends, therefore, that the data from these 12 patients should be excluded from all efficacy analyses of this study.

Thus, an analysis based on first cycle data only and excluding all patients recruited in Center 5 was performed. By that analysis, the difference between groups is 4.2%, and the upper bound of the 95% confidence limit of the estimated difference in hematuria rates is about 15%. If five additional patients who discontinued prematurely (3 in the iv+po group and 2 in the iv group) are also excluded, the upper bound of the confidence limit could be as high as 17%. **These results would suggest that the upper bound of the 95% confidence limit is greater than the required 10% and the study would fail to demonstrate that the two mesna regimens are statistically equivalent.**

Nevertheless, only 1 patient actually had severe hematuria in any of these analyses. For a generally non-lethal toxicity, this would still provide empirical support for efficacy for the iv+po regimen.

Following the sponsor's submission of data on 5 additional patients in February 1998, the FDA statistician re-analyzed the data **using first cycle data only and excluding all patients recruited in Center 5, and the 5 additional patients who discontinued prematurely. This analysis revealed that there were 1/25 (4%) patients with severe hematuria in the iv+po group and 0/29 (0%) patients in the iv group, resulting in a difference of 4% (95% CI: 7.4%, 15.4%). Thus, the upper bound of the 95% confidence limit is substantially greater than 10%, and statistically this study fails to demonstrate that the two mesna regimens are equivalent.**

Of great concern is the statistically significant incidence of death on the iv+po/iv mesna sequence (see Dr. Chen's Statistical Review Tables 1 and 2). As shown in Table 1, the reason for the discontinuation (death) is significantly associated with the assignment of the iv+po/iv sequence (Fisher's exact test, p=0.029). If death is counted as a failure, the patients treated in the iv+po/iv mesna sequence had a significantly higher rate of death than those treated in the mesna iv/iv+po sequence (Fisher's exact test p=0.053, asymptotic test p=0.022). The high death rate in the iv+po/iv sequence is not readily explained, but may have arisen by chance. A higher death rate was not documented in the second controlled study.

2. Study MED504

Title: European Multicenter Randomized Parallel Group Study (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. Four of the centers entered no patients. The names and locations of the investigators are provided below.

Table 21. MED504: Investigators and Locations

Center	Investigator	Location
1*	Seeber	Essen
2*	Scheef	Bonn
3*	Mezger	Bonn
4*	Drings	Heidelberg
5	Voigrmann	Herne
6*	Hoffken	Jena-Lobbeda
7*	Lindecken	Goch
8*	Wickramamayake	Koln
9	Meuthen	Koln
10	Niederle	Leverkusen
11*	Hans	Oberhausen

*Center enrolled at least one patient

This study utilizes the FRC (Fuchs-Rosenthal Chamber) method for evaluation of hematuria. This method analyzes fresh urine under a glass slide with built-in chambers, the bottom of which is demarcated and divided into a total of 256 squares with fixed volumes. A cover glass covers the apparatus. The volume of each chamber is fixed and standardized. Areas are then counted and photographed for counting the number of RBCs per ul of fresh urine. Following a pre-NDA meeting with the Agency, the sponsor re-validated the FRC method and re-analyzed study MED504.

a) Objectives

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. The secondary objective was to compare the safety and tolerability of the two mesna regimens.

b) Rationale

The rationale of the study is similar to the previous study in its intent to establish the safety and efficacy of po mesna. In contrast to the previous study however, the maximum number of RBCs/ul of urine during the 5 days of ifosfamide treatment and the 5 days that followed, rather than the frequency of severe microhematuria and macrohematuria observed during that period, was defined as the primary efficacy parameter.

c) Experimental Design

The experimental design of the study was such that the study was a phase 3, multicenter, randomized, parallel group study designed to evaluate the uroprotective efficacy and safety of iv/iv/iv and iv/po/po mesna regimens in cancer patients receiving treatment with ifosfamide 2.0 g/m^2/day for 5 consecutive days with a 17-day post-treatment follow-up period. The study was divided into two phases: a pilot phase and a main phase. The objective of the pilot phase was to investigate the variance of the primary parameter, i.e., the maximum grade (somewhat different than the maximum number of RBCs) of hematuria. The results of the pilot phase were used to determine the sample size for the main phase. Patients who met all inclusion criteria were randomized to receive one of the following two mesna regimens-iv/iv/iv at 20% of the ifosfamide dose iv at 0, 4 and 8 hours, or iv/po/po at 20% of the ifosfamide dose (iv) at 0 hours and 40% of the ifosfamide dose po at 2 hours and at 6 hours. Standard ampoules were utilized for iv injection, while 400 mg [redacted] film-coated tablets were used for the po part of the study. Randomization was centrally controlled. The actual po dose was rounded down to the next 200 mg dose as tablets were scored. Intravenous mesna could be used as salvage in the event a patient vomited within 2 hours after po dosing. If a patient vomited twice within 2 hours after oral dosing within one cycle that patient was to be considered a treatment failure. Treatment was not blinded. A standard degree of hydration was maintained.

Selected inclusion and exclusion criteria are replicated below.

Table 22. Selected Criteria for Inclusion and Exclusion

Inclusion criteria
• Histologically confirmed malignancy
• Signed written consent form
• ECOG performance status 0, 1, or 2
• Scheduled to receive at least one cycle of ifosfamide chemotherapy at a constant daily dose of 2.0 g/m^2 given as an iv infusion over 30 to 60 minute for 5 consecutive days as monotherapy or part of combination chemotherapy
• Age $\geq$ 18 years
Exclusion criteria
• Urothelial carcinoma, prostate cancer, cancer of the seminal vesicles, resection of the stomach or bowels, or nephrectomy
• Chronic hemorrhagic cystitis during the last 6 months
• > 200 RBCs/ul (or > 20 RBCs/hpf) 7 days prior to the study
• Non-drug therapy 7 days prior to and during the study with the potential to cause hematuria, e.g., indwelling urinary catheter, transurethral biopsy, etc.

Ifosfamide was administered with concurrent mesna on days 1-5. The following were performed on days 1-5, days 6-10 and days 11-15 of one cycle: urinalysis, hematuria assessment using the Fuchs-Rosenthal Chamber, adverse events.

d) Study Endpoints

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 ifosfamide regimen and the 5 days of post-treatment follow-up, using the FRC method with photo-counting. Urinary RBC concentrations of 10 RBCs/hpf (=100 RBCs/ul) were used to determine if mesna tablets could successfully mitigate the urotoxicity of ifosfamide. A difference or shift of 100 RBCs/ul between the approved iv/iv/iv regimen and the experimental iv/po/po regimen was chosen as the criterion used to differentiate the two study drug regimens. The uroprotective efficacy of the two mesna regimens was to be considered equivalent if the frequency of urinary RBCs observed with the iv/po/po regimen was at least comparable to that observed with the iv/iv/iv regimen, allowing for a difference of up to 100 RBCs/ul with respect to the shift of the primary parameter of uroprotective efficacy between the two regimens.

The secondary outcome parameters of efficacy were the maximum number of RBCs in the urine (RBCs/ul on days 2-10) based on direct microscopic counting as determined by dipstick, and the maximum RBCs/hpf on days 2-10 as determined by routine clinical urine sediment urinalysis.

The primary outcome measures of safety consisted of adverse events, laboratory test results, and vital sign data.

Statistical Consultation: The results of the statistical analysis and consultation will be described below. See Dr. Gang Chen's Statistical Review for additional details.

As provided by the sponsor, the efficacy of the iv/po/po regimen vs the iv/iv/iv regimen was evaluated by the Wilcoxon-Mann-Whitney test, the Hodges-Lehmann estimator, and Clopper-Pearson confidence intervals. The safety aspects of the study were evaluated using Clopper-Pearson confidence intervals. Fifty-four patients were randomized. Two patients randomized to the iv/po/po regimen withdrew from the trial before receiving study drug. In the intent-to-treat population, 50 patients were evaluable for the primary efficacy parameter and most patients were evaluable for analysis of the secondary efficacy parameters. The analysis of safety data was based on the intent-to treat population, excluding two patients who did not receive the study drug.

e) Study Results

(1) Demographics, Protocol Deviations

A total of 54 patients was recruited for the study and randomized to treatment with either regimen (n=27). Of the 52 patients who received the study medication, four (8%) were discontinued prematurely from the study. Patient 8/57 (iv/po/po) and 6/88 (iv/iv/iv) died from progression of disease after receiving the second dose of ifosfamide; patient 8/59 (iv/iv/iv) withdrew her consent to participate in the study after day 5; and patient 11/104 (iv/iv/iv) was forced to discontinue therapy due to severe leukopenia.

Deviations from the protocol are summarized below as presented by the sponsor (each patient with more than one deviation has been counted for each of the applicable deviations). While the protocol deviations resulted in the exclusion of patients from the per-protocol population, the protocol deviations involved were not major and did not compromise the intent-to-treat analysis of efficacy.

Table 23. Summary of Deviations from Protocol - All Patients Treated

Deviation:	Mesna iv/iv/iv	Mesna iv/po/po
Increased hydration (above protocol limits)	9	5
Decreased hydration (below protocol limits)	7	5
Administration of mesna dose 30-65 min before ifosfamide	6	5
Duration of ifosfamide infusion < 30 min	4	3
Duration of ifosfamide infusion > 90 min	3	2
Missing photographs on > 2 consecutive days*	2	4
Time of mesna administration not recorded	2	0
Ifosfamide dose too low*	2	1
Incorrect mesna regimen administered	0	1**
IV mesna taken orally and dose too low*	1	0
Mesna dose too low*	0	1
Presence of urinary catheter*	1	0

*Excluded from per-protocol analysis

**Patient 3/31 was randomized to the iv/po/po regimen but received the iv/iv/iv regimen. This patient was included as treated with iv/iv/iv mesna in the intent-to-treat analysis, but excluded from the per-protocol analysis.

With respect to the intent-to-treat population, 52 patients (27 on iv/iv/iv; and 25 on iv/po/po) who received at least one dose of study drug were included. These patients were also included in the safety analysis. For the primary efficacy parameter (the maximum number of RBCs/ul of urine based on FRC photo-counting over days 2-10), patients 7/25 and 3/36 (both in the iv/po/po group) had to be excluded because of lost photo-counts.

In the per-protocol population, 15 patients (9 on iv/iv/iv; and 6 on iv/po/po) were excluded from the per-protocol analysis and included only in the intent-to-treat analysis. The listing of patients excluded from the per-protocol analysis and the reason or reasons for exclusion are provided by the sponsor as follows.

Table 24. Reasons for Exclusion from the Per-Protocol Analysis

Patient(s)	Reason(s)
8/57, 6/68, 8/59, 11/104	Discontinued from the study prematurely
2/17, 2/18, 11/99	Dose of ifosfamide too low
3/31	Randomized to iv/po/po but received iv/iv/iv
3/32	Urinary catheter; > 2 successive daily RBC counts missing
3/36, 7/25, 11/10, 11/97	All photos missing on > 2 consecutive days
4/73	Received only 50% of the planned mesna dose
11/103	Drank the 3rd mesna dose on days 3 & 4 instead of receiving it iv; considered to be under-dosed since the relative bioavailability of oral mesna is 50%

Therefore, only 18 patients in the iv/iv/iv and 19 patients in the iv/po/po group were included in the per-protocol analysis.

With respect to the demographic data, the intent-to-treat population consisted of 20 (38%) female and 32 (62%) male patients. In the iv/iv/iv treatment group there were 12 (44%) female and 15 (56%) male patients. For the iv/po/po group the respective figures were 8 (32%) and 17 (68%) male patients. The treatment groups were similar with respect to the means and medians of age, weight, height and body surface area. Prior chemotherapy regimens in the intent-to-treat analysis consisted of vindesine 7 vs. 5, etoposide 4 vs 4, adriblastine/DTIC 1 vs 0, adriblastine/carboplatin 0 vs 1, doxorubicin 2 vs 1, and mitomycin C 0 vs 1, in the iv/iv/iv vs iv/po/po arms, respectively.

Five patients received a higher dose of ifosfamide (2.1-2.5 gm/m^2) than that required by the protocol. Two of these patients were excluded from the per-protocol analysis for other reasons. The remaining 3 patients (2 on iv/po/po and 1 on iv/iv/iv) were considered to have a higher risk of developing hematuria but were not excluded from the per-protocol analysis. At Center 3, 4 patients (2 in each arm) did not receive a constant daily dose of ifosfamide. The deviations from the calculated dose of ifosfamide per day were between 4% and 9% and were considered to have little effect on the risk for hematuria.

Concomitant medications consisted of N-acetylcysteine, antiemetics, antidiarrheals, laxatives, other gastrointestinal drugs, glucocorticoids, heparin (6 in the iv/iv/iv and 4 in the iv/po/po arms), morphine and codeine. There were no major differences between treatment groups with respect to the use of concomitant drugs except for laxatives, gastro-intestinal drugs and perhaps heparin. It was felt that the study was not confounded by concomitant medications used in the intent-to-treat population. Concurrent illnesses

were not expected to confound the evaluation of the efficacy and safety endpoints of the study.

With respect to hydration, at four centers oral intake was not always recorded and hydration data was missing for days 3, 4, and 5 for patients 6/68 (iv/iv/iv), 8/57 (iv/po/po) and 11/104 (iv/iv/iv). In both the intent-to-treat and per-protocol populations, there was no difference between the two mesna treatment groups with respect to the amount of hydration or the number and types of deviations from the hydration regimen required by protocol (i.e., mean urinary specific gravitates in the two arms were similar in the two groups). In both the intent-to-treat population and in the per-protocol populations, the mean (+/- SD) maximum fluid intake, range of mean fluid intake (ml) on days 1-5, and range of mean urinary specific gravity on days 1-10 were similar.

With respect to the homogeneity and missing patterns of hematuria data across treatment groups and centers, no formal statistical testing was performed. However, inspection of the demographic data and the baseline number of RBCs/ul at day 1 revealed no major differences between the treatment groups and only minor exceptions among the centers. Homogeneity of the two treatment groups was also checked by comparing the distributions of missing RBC photo-count data. The days without photo-counts for any reason excluding the missing photo-count days for the patients who died on day 2 (6/88 on iv/iv/iv and 8/57 on iv/po/po) and for patient 8/59 who withdrew consent on day 5 are summarized below as presented by the sponsor.

Table 25. Treatment Groups: Missing Photo-count Data

Treatment Group	Intent-to-Treat Population	Per-Protocol Population
iv/iv/iv	32 days/257=12%	11 days/180=6%
	**18 days/257=7%	**5days/180=3%
iv/po/po	43 days/242=18%	20days/190=11%
	**4 days/242=2%	**7days/190=4%

**missing photo-count days without any other hematuria measurement (direct microscopic counting, dipstick, or urinary sediment)

(2) Efficacy Results: Hematuria

The primary efficacy parameter was the maximum number of RBCs in urine (RBCs/ul, as determined by FRC photo-counting) during 9 consecutive days following day 1or the first dose of ifosfamide and mesna. The sponsor utilized the intent-to-treat analysis (data for 52 patients, excluding 2 patients who did not receive the study medication, both in the iv/po/po group) as the primary analysis, and the per-protocol analysis (including data for 37 patients) as a confirmatory analysis. The presence of 20 RBCs/ul (equivalent to 2 RBCs/hpf) was assumed to reflect physiological RBC excretion (measured on day 1 before starting ifosfamide). At baseline, 47/51 (92%) of patients - 47/52 by this reviewer's count - had less than 20 RBC/ul, three iv/iv/iv patients had RBC/ul values of 53, 47, and 49, and one iv/po/po patient had a baseline RBC/ul value of 45.

In both the intent-to-treat and per-protocol populations, 78% of patients in the iv/iv/iv group and 95% of patients in the iv/po/po had maximum RBC counts in urine below 50

RBCs/ul, indicating that the mesna and iv/iv/iv and iv/po/po regimens were equally effective in protecting patients from ifosfamide urotoxicity, as shown below.

Table 26. Categorized RBC Count (RBCs/ul) by Treatment Group - Intent-to-Treat and Per-Protocol Populations

Categorized RBC Count (RBCs/ul)*	<20	20 to <50	50 to < 100	100 to <500	500 to <1000	>1000	Total
Max over Days 2-10	N	N	N	N	N	N	N
Intent-to-Treat Population							
Mesna iv/iv/iv	14	7	3	2	0	1	27
Mesna iv/po/po	12	10	0	0	1	0	23
Per-protocol Population							
Mesna iv/iv/iv	10	4	1	2	0	1	18
Mesna iv/po/po	9	9	0	0	1	0	19

*Determined by FRC Method (photo-counting)

One patient in the iv/iv/iv group had a hematuria > 3000 RBCs/ul (ifosfamide treatment was withheld on day 5; patient hospitalized until hematuria resolved), and one patient in the iv/po/po group had a severe microhematuria of > 500 RBCs/ul, however ifosfamide treatment was continued. These findings suggest the need for evaluating the maximum number of RBCs in the urine daily while on ifosfamide treatment.

Interestingly, in both the intent-to-treat and per-protocol populations, the maximum RBC values tended to occur early in the treatment (days 2 and 3) and late in treatment (day 8). In the per-protocol population, 9/18 patients in the iv/iv/iv group and 13/19 patients in the iv/po/po group had the maximum number of RBCs excreted after the last day of ifosfamide/mesna treatment. There were no clinically significant differences between the mesna iv/iv/iv and iv/po/po regimens with respect to the distribution of maximum RBC values as measured over 9 consecutive days of treatment (i.e., days 2-10).

The sponsor's results of the between group comparisons of the maximum number of RBCs as determined by the FRC method are summarized in the table below.

Table 27. Between-Group Comparisons of Maximum RBCs/ul by FRC Photo-count Method Intent-to-Treat and Per-Protocol Populations

	N		Maximum RBCs/ul (photo-counts)				p-value
			Hodges-Lehmann estimator	Lower 95% confidence limit	Upper 95% confidence limit	Upper 95% confidence limit	Wilcoxon-Mann-Whitney test
Population	iv	po		two-sided	two-sided	one-sided	one-sided
Intent-to-treat population	27	23	0.0	-11.0	8.0	7.0	<0.0001
Per-protocol	18	19	3.0	-11.0	14.0	11.0	<0.0001

In the intent-to-treat population, the Hodges-Lehmann estimator is 0.0 RBCs/ul, indicating no difference between the treatment groups with respect to the median of the maximum RBC value for each patient on each of the 9 consecutive days following the start of ifosfamide treatment (days 2-10). **The upper limit of the one-sided 95% confidence interval is 7 RBCs/ul which is markedly less than the 100 RBCs/ul selected *a priori* as a medically relevant difference and the predefined therapeutic equivalence bound.** The sponsor indicates that these findings demonstrate the uroprotective equivalence of the iv/po/po and iv/iv/iv mesna regimens.

In the per-protocol confirmatory analysis, the Hodges-Lehmann estimator is 3.0 RBCs/ul, also indicating that there is no statistically significant difference between the treatment groups with respect to the median maximum RBC value on each of the 9 days following the start of ifosfamide treatment. The upper limit of the one-sided 95% confidence interval is 11 RBCs/ul which is still well below the pre-defined uroprotective equivalence bound, indicating per-protocol confirmation of the intent-to-treat analysis.

The p-value of the one-sided Wilcoxon-Mann-Whitney test ($p<.0001$) also was felt to demonstrate uroprotective equivalence for both the intent-to-treat and per-protocol populations. Sensitivity analyses performed by the sponsor considering the accuracy and precision of the photo-counting of low RBC/ul concentrations using the FRC method, were also supportive.

Several secondary efficacy parameters were also compared for patients receiving the iv/iv/iv and iv/po/po mesna regimens. These included the maximum number of RBCs in uncentrifuged urine on each of 9 consecutive days based on direct microscopic counting in the FRC (intent-to-treat population: N=52), the maximum RBCs/ul on days 2-10 as determined by dipstick in uncentrifuged urine (intent-to-treat population: N=52), and the maximum RBCs/hpf as determined by routine clinical urine sediment analysis (intent-to-treat population: N=43). In addition, other secondary efficacy analyses included comparisons of the frequency of hematuria grades in the two treatment groups, the median and mean daily excretion of RBCs in urine, and day of maximum RBC values in the iv/iv/iv and iv/po/po mesna regimens.

The statistical analyses for maximum RBCs/ul by direct microscopic counting and by the dipstick method utilizing the Hodges-Lehmann estimators indicated uroprotective equivalence between the two mesna regimens in both the intent-to-treat population and the per-protocol populations.

Analysis of urine sediment was optional and not performed in all patients, however, the results of this analysis (the method used most commonly in clinical practice to detect hematuria) were consistent with the results obtained using the FRC method to compare the maximum number of RBCs/ul detected in the two treatment groups on days 2-10.

The evaluation of the frequency of hematuria grades was confounded by the fact that approximately 50% of the patients in both groups had <20 RBCs/ul (i.e., normal RBC excretion), and another 30% of patients in the iv/iv/iv group and 40% in the iv/po/po group had less than 100 RBCs/ul. Thus, the originally proposed categories in the protocol seemed inappropriate to characterize the extent of uroprotection achieved with mesna (e.g., Grade 1 hematuria = 0 to 200 RBCs/ul). Using the (re-defined) hematuria categories shown above in Table 26, there was one patient on the iv/iv/iv arm who had Level 6 hematuria (>1000 RBCs/ul) and one patient on the iv/po/po arm who had Level 5 hematuria (500 to <1000 RBCs/ul).

Median values of daily excretion of RBCs in the urine were not significantly different in the two analyses of the two treatment arms. All median values of RBCs/ul in both treatment groups were within the physiological range of RBC excretion (<20 RBCs/ul) and only minor changes occurred during the study period.

The sponsor's global assessment of efficacy is that equivalent uroprotection was observed with the two mesna regimens in all analyses of the maximum number of RBCs/ul using all specified methods. Only two patients (one in each group) in the intent-to-treat population experienced maximum hematuria > 500 RBCs/ul.

(3) Safety Evaluation

In the sponsor's evaluation of safety, 27 patients in the mesna iv/iv/iv group and 25 patients in the iv/po/po group were evaluated for safety. The incidence of ADEs was 74% and 76%, and the incidence of ADRs was 55% and 44%, in the two mesna groups, respectively.

The most frequent ADEs were gastro-intestinal in nature (nausea, vomiting) and leukopenia. Nausea was noted in 12/27 (44.4%) of the iv/iv/iv patients and in 14/25 (56%) of the iv/po/po patients. Vomiting occurred in 7/27 (29.6%) in the iv/iv/iv group and in 7/25 (28%) in the iv/po/po group.

Leukopenia <1000 WBCs/ul measured on days 8 and 15 was found in 8/27 (29%) in the iv/iv/iv group and in 6/25 (24%) in the iv/po/po group. The incidence of leukopenia classified according to the SWOG Criteria is replicated as provided by the sponsor below. The iv/po/po arm did not appear to have a greater incidence of severe leukopenia. The sponsor suggested that the antiproliferative effect of ifosfamide as reflected by leukopenia is not affected by the po mesna regimen.

Table 28. Incidence of Leukopenia (SWOG Criteria)

	Schedule	WBCs/ul					Total
		>4000	3000 to <4000	2000 to <3000	1000 to <2000	<1000	
All patients	iv/iv/iv	4	6	4	5	8	27
	iv/po/po	1	4	8	6	6	25
Monotherapy (ifosfamide only)	iv/iv/iv	2	3	3	1	4	13
	iv/po/po	0	1	5	3	4	13
Combination chemotherapy	iv/iv/iv	2	3	1	4	4	14
	iv/po/po	1	3	3	3	2	12

There were 3 deaths on the iv/iv/iv arm (sepsis, progressive disease, and "rapid worsening of patient's general condition" and one death in the iv/po/po arm attributed to the primary disease and not the study medication. (This represents the converse circumstance as noted in the previous study D-07093-0018 in which more of the iv+po patients died).

Serious adverse events were observed in 6 patients (four in the iv/iv/iv and two in the iv/po/po groups). All serious adverse events, with the exception of macrohematuria in patient 6/67 were considered to be unrelated to study drug. Bone marrow depression is a known complication of treatment with ifosfamide and other cytotoxic agents. These events are briefly described below:

Patient 2/20 (iv/iv/iv): The patient had life-threatening bone marrow depression and required transfusion of RBCs.

Patient 6/67 (iv/iv/iv): The patient developed a hematuria of >3000 RBCs/ul as noted above. Ifosfamide was stopped on day 5. In contrast to the recommendations of the study protocol, mesna treatment was also stopped on day 5. The patient's symptoms resolved without further measures.

Patient 11/103 (iv/iv/iv): The patient had life-threatening leukopenia and fever and required parenteral antibiotics.

Patient 11/111 (iv/iv/iv): The patient suffered from life-threatening leukopenia and developed pneumonia, requiring parenteral antibiotics.

Patient 3/36 (iv/po/po): The patient was hospitalized for severe leukopenia and treated with G-CSF. No infection was diagnosed.

Patient 11/113 (iv/po/po): The patient was hospitalized for treatment of a stroke, which was potentially life-threatening. The patient recovered without major complications.

There were no clinically significant changes in BP or heart rate in the study in either of the two mesna groups. There appeared on retrospective review to be no significant differences in ECOG performance status between the two groups.

The sponsor notes no difference between the mesna groups with respect to the degree and frequency of erythrocyte count, hemoglobin level and platelet count decreases during the study. Thrombocytopenia is particularly germane to the issue of hematuria and to the issue of toxicity of the two treatment arms. Four of the 27 iv/iv/iv patients and 3 of the 25 iv/po/po patients had low platelet counts during the study. Of the iv/po/po patients who developed thrombocytopenia, one patient developed hematuria during days 3-5, however, a platelet count of 89,000/ul was noted only on day 10, at which time hematuria had already resolved. The second patient had low platelet counts secondary to marrow infiltration, and the third patient had normal RBC excretion on all study days except for day 6 (46 RBCs/ul noted). Thus, there appeared to be no clear correlation between thrombocyopenia and the development of hematuria in the iv/po/po group.

In both treatment groups, the sponsor noted that there was a moderate increase in BUN of about 30-50% on days 8 and 10 with a return to previous values at the end of the study (day 22). This was slightly more pronounced in the iv/iv/iv group. Serum creatinine levels were also transiently elevated by about 20% on days 8 and 10 in both treatment groups. No differences could be detected between the mesna regimens with respect to clinical chemistry values.

The sponsor's global assessment of tolerability indicated that the two mesna regimens were comparable and generally well tolerated. Only one case of hematuria greater than 3000 RBCs/ul in the iv/iv/iv arm occurred and only one case of severe microhematuria occurred in the iv/po/po group. Severe leukopenia occurred equally (<1000 WBCs/ul) on both regimens. Though the sponsor concludes that the number of patients is small, the

above findings suggest that the antiproliferative, leukopenic activity of ifosfamide is not affected by either mesna regimen.

(4) FDA Evaluation

Study MED504 was a Phase 3 multicenter randomized, parallel study designed to investigate the uroprotective ability and safety of an experimental regimen of iv/po/po mesna vs an iv/iv/iv (approved) regimen of mesna in patients undergoing treatment with ifosfamide at a dose of 2 gm/m^2 per day for 5 days. Follow-up lasted 17 days post-treatment. A total of 54 patients was enrolled in the trial, with 27 patients in each arm. Two patients randomized to the iv/po/po arm did not receive the study drug. Therefore, 52 patients (27/52 on iv/iv/iv and 25/52 on iv/po/po) who received at least one dose of the study drug were included in the intent-to-treat analysis.

Significantly, two additional patients in the iv/po/po group were excluded from the primary efficacy analysis because all photo-counts were missing. Thus, only 18 patients in the iv/iv/iv group and 19 patients in the iv/po/po group were included in the per-protocol analysis as 15 patients (9 on iv/iv/iv and 6 on iv/po/po) were excluded from the per-protocol analysis and included only in the intent-to-treat analysis. This represents a significant patient loss and a potential confounding source for study evaluation.

Table 23 above presents a summary of deviations from protocol in all patients treated. Though the deviations appear to be reasonably matched in the two arms, these deviations resulted in the exclusion of 6 patients in the iv/iv/iv arm and 6 patients in the iv/po/po arm from the per-protocol analysis.

In consultation with the FDA Statistician, 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 in this study was below the detection limit (<20 RBCs/ul, by photo-count). **Therefore, the statistical hypotheses and procedures (i.e., Wilcoxon-Mann-Whitney test) used by the sponsor for such data could be considered invalid.**

In the sponsor's evaluation, in both the intent-to-treat and per-protocol populations, 22% of the patients in the iv/iv/iv group, and 5% of the patients in the iv/po/po group had maximum RBC counts in the urine over 50 RBCs/ul (i.e., abnormal levels). Analysis by the FDA statistical reviewer utilizing a Fisher's exact test for both populations showed that the mesna iv/iv/iv and iv/po/po regimens were equally effective (see below).

Though the study is small and badly flawed with respect to missing data and patient dropouts it supports the uroprotective equivalence of iv+po mesna vs iv mesna alone.

Table 29. 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 (22.2%)	-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 5 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 rather than diminishing it is somewhat assuaged.

Impacting on the concern that po mesna may enhance ifosfamide toxicity is the observation that on day 10, leukocytes fell from baseline to a mean of 1043 vs 1342 on the iv/po/po and the iv/iv/iv arms, respectively; neutrophils fell to 18% vs 27% respectively, and platelet counts fell to 185,556/ul vs 202,455 on the two arms, respectively. In all significant hematological parameters there appeared to be a lower count in the po arm on the designated nadir day, raising concern of toxicity enhancement rather than toxicity diminution. (see Sponsor's Table 3.5.1.4-8, Appendix C).

3. Reviewer's Overall Summary and Conclusions of Controlled Studies

In the US study (D-07093-0018), both the intent-to-treat and the per-protocol analyses of the sponsor indicated that mesna administered by either the iv/po/po or the standard iv/iv/iv regimen was equivalent in terms of providing uroprotection from ifosfamide when given in doses that are clinically relevant. The analyses performed by the FDA Medical and Statistical Reviewers showed that there was a high percentage of loss of subjects and data in the study. The one-sided upper bound for the 95% confidence limit for the difference in severe hematuria rates between the two regimens was greater than 10%, which does not support statistical bioequivalence. Thus, at best, it can be said that the uroprotection provided by the two regimens is similar, but not equivalent.

Of concern in the above study was a statistically significant higher rate of death in the mesna iv+po/iv sequence compared to the iv/iv+po sequence. Though this finding is somewhat mitigated by the second controlled study in which more deaths occurred in the iv/iv/iv arm than in the iv/po/po arm, the sponsor should endeavor to discern whether oral mesna may enhance toxicity.

In the German study (MED504), the maximum number of RBCs/ul following ifosfamide treatment, rather than the rate of severe hematuria, was selected as the primary parameter of efficacy. A two-sided confidence interval for the difference between the iv/iv/iv and

iv/po/po regimens of (-11, 8) in the intent-to-treat analysis indicates uroprotective equivalence of the two mesna arms. The limitation of the FRC method of photo-counting was that patients with urinary RBC counts less than 20 RBCs/ul were truncated at a RBC count of 20 RBCs/ul. Statistical review by the Agency categorized RBC counts as RBCs/ul > 50 vs < 50 RBCs/ul and by treatment group. (See Statistical Review Table 9). That review documented the protective efficacy of mesna iv/po/po as not being inferior to that of the mesna iv/iv/iv regimen (95% CI: -40%, 4%) in the intent-to-treat population.

The evidence from these controlled trials together with the data from urinary PK evaluation in 11 patients in study D-07093-0018 support the sponsor's proposal for intravenous plus oral mesna dosing to provide uroprotection for ifosfamide.

B. Uncontrolled Studies

1. Study D-07093-0019

Multiple Dose Urinary and Serum Pharmacokinetics of Mesna and Dimesna After Oral and Intravenous Administration to Patients Treated with Ifosfamide

Investigator: Johnson, DH, Vanderbilt University Medical Center, Nashville, TN

This study was listed as an open, randomized, cross-over within cycle, controlled study by the sponsor. In point of fact, there were only 7 patients on the iv/po/po arm and 6 patients on the iv/iv/iv arm. Five patients in the iv/iv/iv arm dropped out. The sponsor maintains that no patients demonstrated any evidence of hematuria during treatment as measured by urine sediment analysis (RBCs/hpf).

a) Objectives

To assess the urinary PK equivalence and uroprotection of two dosing regimens of mesna (iv only vs iv+po) administered to cancer patients receiving ifosfamide.

b) Study Design

The study was a multiple-dose, randomized, open-label, cross-over, bioavailability study. The iv+po dosing test regimen consisted of one dose of iv mesna (20% of the ifosfamide dose) given at 0 hours, followed by two po doses of 300 mg [redacted] film-coated mesna tablets (each equivalent to 40% of the ifosfamide dose) given at 2 and 8 hours after the start of the iv dose of mesna. The iv reference regimen was the approved mesna injection regimen consisting of three iv mesna doses (each equivalent to 20% of the ifosfamide dose) given at 0, 4, and 8 hours. All patients included in the PK calculations received both regimens in a randomized cross-over fashion in that patients were randomly assigned to receive either the iv standard regimen on day 1of their 5-day chemotherapy cycle and the iv+po test regimen on days 2-5 (arm A) or to the iv+po test regimen on day 1and the iv reference regimen on days 2-5 (arm B).

The inclusion criteria for this study were: males or females, aged 18-75, pathologically confirmed diagnosis of non-oat cell lung carcinoma, receiving or scheduled to receive at

least two cycles of ifosfamide (iv) at a dose of 1.2 gm/m^2/d for 5 days, and etoposide 50 mg/m^2 (po) for 21 days, meeting normal organ function criteria etc., ECOG performance status of 0 or 1, no previous chemotherapy, and no concurrent radiotherapy.

The criteria for evaluation were pharmacokinetic - the primary endpoint of the urinary PK evaluation was the cumulative urinary excretion (CUE), maximum urinary excretion rate (R_{max}), and minimal urinary concentration (C_{min}) from 12 to 24 hours, following the first dose of mesna. The plasma PK parameters evaluated were AUC_{0-t}, AUC $_{0-inf}$, and C_{max}, as well as safety (i.e., the assessment of laboratory and vital parameters and monitoring of adverse events).

The statistical methods utilized by the sponsor consisted of ANOVA. Incidences of adverse events were calculated along with screening for remarkable changes. A total of 13 patients were recruited, 12 for the PK analysis; 13 males, aged 40-79 years.

c) Conclusions

(1) Sponsor

The sponsor concluded that none of the patients in the study demonstrated any evidence of hematuria during the study and that therefore both treatment regimens successfully prevented the hematuria associated with the use of ifosfamide chemotherapy. None of the adverse experiences reported were felt by the sponsor to be associated with the use of mesna. None of the changes, other than a decrease in leukocytes (felt to be associated with the chemotherapy), were consistent nor showed definite trends. Therefore, the sponsor concluded that patients receiving ifosfamide could be safely and efficiently treated with a regimen of mesna using an initial infusion followed in 2 hours and 8 hours later with oral doses of mesna.

The PK analysis of the sponsor indicated that the urinary excretion of mesna and dimesna was similar for both regimens. The iv+po regimen resulted in a greater persistency of mesna/dimesna in urine (i.e., significantly greater urinary C_{min}). It was felt that the persistency suggested some carryover effect from day to day, consistent with some drug accumulation. PK analysis of the plasma data indicated that the AUC_{0-t} after the iv+po regimen was 60% of that following treatment with the iv regimen. C_{max} for the iv+po regimen was 62% of that for the iv regimen. This data supported the absolute bioavailability of the iv+po regimen of 40%. The sponsor stated that because of the small number of patients and the limited number of observations in each regimen, differences between regimens must be interpreted cautiously. They indicated that the objectives of the study were met because of the similarity of the cumulative urinary excretion between the two regimens.

(2) FDA

Of the 13 patients enrolled in the study (7 in the arm A and 6 in arm B) there were 5 dropouts in arm B. In the PK section of the evaluation, there were multiple missing data points. More patients in arm A than arm B experienced nausea (5/7 vs 2/6), constipation (3/7 vs 0/6), and vomiting (3/7 vs 1/6). There were 23 incidents reported in arm A vs 10

incidents in arm B. Little can be said regarding myelosuppression. No patient experienced above grade I hematuria but only 9 of 13 patients were evaluated.

The conclusion of the FDA Biopharmaceutics Reviewer, John Duan, Ph.D., was that the iv+po regimen resulted in a greater persistency of mesna and dimesna in the plasma and urine as characterized by a significantly greater urinary C_{min}. Therefore, this study supported the sponsor's proposal that mesna given in the iv+po dosing schedule be administered at the time of ifosfamide infusion, and at 2 and 6 hours later. The FDA Biopharmaceutics Reviewer further noted that the small number of patients and limited number of observations in each regimen and the parallel design of the comparison resulted in a very low power statistically for the PK evaluation. Only one iv+po patient had a terminal log-linear phase in the plasma concentration vs time profile. Therefore, the plasma PK data was felt not to be reliable. Lastly, the study did not use the to-be marketed preparation, but it did provide information to modify the oral dosing regimen and bioequivalence for that preparation ultimately marketed.

The small number of patients and the limited number of observations in each regimen made interpretation of the study results difficult. In addition, this study did not use the to-be marketed drug formulation, nor the proposed dosing regimen for iv+po (i.e., dosing at 0, 2, and 6 hours). This study provides limited support of safety and efficacy.

2. Study 07093-0016

Clinical Phase II Trial to Evaluate the Uroprotective Effect of Mesna Film-coated Tablets (600 mg) in Intravenous Ifosfamide Schedules

This study was a phase 2 open, uncontrolled multicenter trial performed between 1992 and 1994 in a planned 188 subjects performed with the objectives of evaluating the uroprotective effect of mesna when administered as a combination of injection solution and [redacted] film-coated tablets, and to assess the tolerability of that mesna regimen. The eligibility criteria were standard compared to previously described trials. The trial required that subjects were to receive ifosfamide iv at doses between 1.2 and 2.5 gm/m^2 given as monotherapy or as part of a combination therapy.

On the day of ifosfamide treatment (given by various schedules but in most cases via a 5-day schedule), patients received mesna film-coated tablets given at 2 and 6 hours after the ifosfamide infusion in a dosage of 40% of the ifosfamide dose (rounded up to the nearest 300 mg or 1/2 of a scored [redacted] film-coated 600 mg tablet) with the usual dose of iv mesna at the time of ifosfamide administration. Generally, mesna was given for 3, 4, or 5 consecutive days. In the protocol, only one treatment cycle was anticipated, however an amendment to the protocol allowed for additional treatment cycles.

All patients who received at least one dose of mesna were included in the analysis of tolerability and for the intent-to-treat analysis. Patients with no protocol violations were included in the per-protocol analysis. Uroprotective efficacy was analyzed only in patients with sufficient protocol adherence. Statistical analysis was by descriptive analysis using point and interval estimators, crude incidence rates, etc.

a) Sponsor's Evaluation

A total of 166 patients entered the study and were eligible for a planned interim analysis. An additional 22 patients were included for a total of 188 for the final evaluation. As urinary dipstick proved unreliable in the first 19 patients (i.e., mesna induced false +'s and false -'s), dipstick analysis was replaced by microscopic analysis and the corresponding patients were excluded from the per-protocol analysis for the uroprotective efficacy of mesna. An additional 35 patients were excluded from the per-protocol analysis due to incomplete serial urinalysis. All 188 patients were included in the intent-to-treat analysis of efficacy and tolerability.

No patient developed macrohematuria during the study. Eight of 188 (4%) patients developed a severe grade III microhematuria (>50 RBCs/hpf). The sponsor concluded that only rare cases of hematuria are to be expected with the proposed schedule of iv/po/po mesna and that the uroprotective effect and tolerability of orally administered mesna 600 mg film-coated tablets was excellent.

b) FDA Evaluation

The tablets used in this uncontrolled study were not of the same strength as the tablets proposed for the NDA and for marketing, and the methodology for evaluating hematuria during the study differs from that of the controlled US study D-07093-0018. The number of inevaluable patients secondary to incomplete urinalysis in this study is also unacceptably high. This study lends limited support for the uroprotective efficacy of oral mesna.

3. Study MED700

Open Multiple Dose Study of the Efficacy and Safety of a Regimen of Mesna Tablets in Patients Treated with Mesna

This study was an open label multicenter trial performed in 7 centers in Germany designed to study the efficacy and tolerability of 400 mg [redacted] film-coated tablets given at 40% of the ifosfamide dose 2 hours prior to, 2 hours following, and 6 hours after ifosfamide given at time 0 hours. Only oral mesna tablets were given in this study. The ifosfamide doses were 1.2-2.0 gm/m^2 daily over 3-5 days.

Patients with histologically confirmed malignancy who were to receive ifosfamide chemotherapy and without other causes present that might be associated with hematuria were recruited and all were available for intent-to-treat analysis. The criteria for evaluation consisted of the maximum number of RBCs/ul of urine (utilizing the photo-count method with FRC, and RBC counting of the unspun urine viewed under a microscope) during days 2 to 10. Adverse events, adverse drug reactions, laboratory test results and physical signs were monitored. Descriptive statistics were used.

Thirty one patients were treated with a 3, 4, or 5 day course of ifosfamide at repetitive doses of 1.2 to 2.0 gm/m^2 given iv over 30-60 minutes as monotherapy or as part of a combination treatment. Fresh morning urine specimens were collected daily during treatment and for up

to 10 days after the start of ifosfamide. Only 16 patients were evaluable for analysis of hematuria and are included in the per-protocol analysis population. Of the patient dropouts, 4 were due to adverse events, 4 to protocol violations, one withdrew consent, and two died for reasons unrelated to mesna. The remaining patient dropouts are unexplained. Interestingly, 9 patients received N-acetyl-cysteine for pulmonary reasons in doses believed to be low enough not to be uroprotective.

Half of the patients in the intent-to-treat and the per-protocol groups had RBCs/ul below the physiological level of excretion (<20 RBCs/ul). No macrohematuria or severe microhematuria (>500 RBCs/ul) occurred in the study. One patient sustained a level of 365 RBCs/ul. The sponsor concluded that the po/po/po mesna regimen was uroprotective, safe and well-tolerated. Adverse events and changes in laboratory values were mainly related to ifosfamide or other medications, and not to the study drug.

Reviewer comment: This poorly executed study, flawed by a large number of dropouts and confounding by the use of N-acetylcysteine provides marginal support for the efficacy of a po/po/po mesna regimen in preventing mesna hemorrhagic cystitis.

C. *Reviewer's Overall Evaluation and Conclusions*

Mesna is chemically, sodium-2-mercaptoethane sulfate. Under NDA # 19-884 mesna for iv injection was approved for the prevention of ifosfamide-induced hemorrhagic cystitis. To prevent the necessity for prolonged hospitalization, an oral formulation was developed. Without tabular structure it was disadvantaged by bad taste. A 300 mg [redacted] film-coated tablet was developed and shown to have activity in studies filed under IND # [redacted] in inhibiting ifosfamide-induced urotoxicity. It was later shown that these tablets sustained decreased dissolution on long-term storage. Later, a 400 mg [redacted] film-coated tablet provided a stable formulation resistant to change in dissolution rate on storage. It is the latter preparation that is the subject of the submitted NDA.

Oral administration of a mesna solution or of Mesnex^{R} Injection has been approved in Canada, Great Britain, and Germany, and mesnex^{R} Tablets have recently been approved in Germany, Great Britain, the Netherlands, Italy and Denmark for the prevention of ifosfamide-induced hemorrhagic cystitis. Below is a global review of the submitted studies.

1. Clinical Pharmacology Studies

Taken as a whole, the pharmacology studies summarized below support the similar urinary excretion patterns of the [redacted] film-coated mesna tablet and of iv mesna. The Biopharmaceutics Review concurs that on the basis of PK data, the 300 mg [redacted] film-coated tablets, the 400 mg and 600 mg [redacted] film-coated tablets, and the mesna injection solution administered orally are bioequivalent.

A. Study D-07093-0007 was a cross-over study conducted to compare the total urinary excretion rates of free thiols and reduced disulfides between mesna drinking ampoules and mesna [redacted] film-coated tablets. In this study, mesna was generally well tolerated with adverse effects consisting of mostly flu-like symptoms. 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.

B. Study D-07093-0008 was a single dose safety, tolerance and PK study comparing the iv injection solution and single ascending oral doses of [redacted] tablets in healthy volunteers. This study was a single-center, open, randomized, Latin square cross-over design Phase 1 study. Headache, nausea, vomiting, general aches, and flushing were noted in the study subjects. 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. The bioavailability of free mesna in the urine after the 600 mg oral dose, the most important parameter for clinical practice, was 67.3% of that for the 600 mg iv dose over 24 hours, and 48.2% for the first 4 hours. The oral doses of 600, 1200 and 2400 mg demonstrated close dose-linearity for the total excretion of mesna and dimesna.

C. Study D-07093-0010 was a multiple dose safety, tolerance and PK study. It was a randomized four-way cross-over Phase 1 study in healthy male volunteers to confirm the results of the single dose trial. The conventional iv schedule of mesna (600 mg three times daily at 0, 4 and 8 hours after ifosfamide) was compared to 2400 mg of mesna [redacted] tablets (300 mg) once daily given at -1 hour, 1200 mg twice daily given at -1 hour and 4 hours, and a combination of iv and oral mesna (600 mg given iv and 1200 mg given po once daily at 0 hours). Skin reactions were the most frequent ADEs reported, followed by gastro-intestinal symptoms including nausea, abdominal colic, diarrhea and flatulence. It was during this study that it was discovered that the [redacted] film-coating hardened, resulting in decreased dissolution. With respect to PK, the excretion of mesna, dimesna and consequently total thiols was slightly higher on day 5 than on day 1 of the oral regimens.

D. Study D-07093-0017 was a single dose bioavailability study of mesna 400 mg [redacted] tablets performed in 25 subjects with the objective of comparing the absolute bioavailability of the 400 mg [redacted] tablet to an iv injection of mesna. In addition, the relative bioavailability of 400 mg [redacted] tablets, 300 mg [redacted] tablets, 600 mg [redacted] tablets and mesna as an oral solution was evaluated. The study was a 5-way cross-over study in healthy volunteers. It was concluded that when given at a dose of 1200 mg, the 400 mg [redacted] tablet was bioequivalent to the 300 mg [redacted] and the 600 mg [redacted] tablets and to the iv solution given po. The [redacted] film-coating did not appear to modify the absorption kinetics of oral mesna.

E. Study 5D-07093-0015 was a Phase 1 open, single-center, randomized 4 way cross-over study of the effect of food on the urinary pharmacokinetics of oral mesna in 12 volunteers. 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 and the orally administered injection solution. Food did not significantly affect tablet absorption.

2. Literature References

The sponsor submitted 75 pertinent literature references addressing the utilization of po mesna (in various forms) in adequate as well as inadequate protective doses in man in which

mesna was provided as a means to attain uroprotection. The submitted selected uncontrolled human studies utilizing various forms of po mesna as well as various combinations of iv and iv+po mesna (generally of an unstated formulation) demonstrated the relative efficacy of oral mesna in preventing the urotoxicity of ifosfamide. It represents a large population experience over many years in numerous countries as reported by a multitude of investigators. This review adds a literature base to support the uroprotective efficacy and safety of oral mesna.

3. Controlled Studies

The sponsor submitted 2 controlled studies in cancer patients receiving ifosfamide chemotherapy. Study D-07093-0018 was a US multicenter open controlled randomized cross-over study comparing iv+po/iv mesna to iv/iv+po. Study MED504 was a German multicenter open, controlled, randomized, parallel group study comparing iv/iv/iv mesna to iv/po/po mesna.

a) Study D-07093-0018

In the intent-to-treat analysis, the sponsor counted all patients who dropped from the study as successes and a re-analysis excluding the 12 patients from center 5 (the subject of an FDA audit) showed that 2% of patients in the iv+po/iv arm and 2% in the iv/iv+po arm had Grade III or IV hematuria. The upper bound of the 95% confidence limit was 6%. The sponsor concluded that excluding the data from Center 5 had no bearing on the overall results.

The FDA Statistical Reviewer felt that counting all patients who dropped from the study as successes was problematic as the loss of subjects complicated analysis and interpretation. With the loss of 41% of patients in the study, it was felt that any analysis based on cycle data may not be valid. An Agency analysis was performed based on first cycle data only, and excluding all 12 patients recruited in Center 5, as well as 5 additional patients who discontinued prematurely. This analysis revealed that there were 1/25 (4%) patients with severe hematuria in the iv+po group, and 0/29 (0%) patients in the iv group, resulting in a difference of 4%, with an upper bound for the 95% confidence limit of 15.4%. Thus, this study would fail to demonstrate that the two mesna regimens are statistically equivalent.

Nevertheless, only 1 patient had severe hematuria in any analysis, suggesting that for a generally non-lethal toxicity, there would be empirical support for the efficacy of the iv+po regimen.

Of additional concern is the high and statistically significant incidence of death in the iv+po group. This high death rate is not readily explained, nor does it occur in study MED 504. With only one episode of grade III or IV hematuria in the experimental arm, this study, in spite of the loss of large numbers of patients, large quantities of data and a high death rate in the iv+po group, could provide support for approval.

b) Study MED504

This study was a Phase 3, multicenter, randomized, parallel group study designed to investigate the uroprotective ability and safety of an iv/iv/iv regimen of mesna vs an

experimental regimen of iv/po/po mesna in patients undergoing treatment with ifosfamide. In this study there were a multitude of dropouts. Out of 28 patients in the iv/iv/iv arm and 26 in the iv/po/po arm, there were only 18 patients evaluable in the former and 19 in the latter for the per-protocol analysis. In this study, contrary to the previous study, there were 3 deaths in the iv/iv/iv arm vs one death in the iv/po/po arm. Thus, the concern that po administration of mesna may be enhancing toxicity rather than diminishing it is somewhat assuaged (see cysteine discussion below).

Impacting on the concern that po mesna may enhance ifosfamide toxicity is the observation that on day 10, leukocytes fell from baseline to a mean of 1043 vs 1342 on the iv/po/po and the iv/iv/iv arms, respectively; neutrophils fell to 18% vs 27 % respectively, and platelet counts fell to 185,556/ul vs 202,455 on the two arms, respectively. In all significant hematological parameters there appears to be a lower count in the po arm on the designated nadir day, raising concern of toxicity enhancement rather than toxicity diminution.

Lastly, the FDA Statistician raised the issue that use by the sponsor of the Wilcoxin-Mann-Whitney test may be inappropriate. It was felt that the urine RBC concentration should be considered a continuous parameter since the maximum numbers of RBCs/ul for approximately 50% of the patients in this study were below the detection limit (<20 RBCs/ul, by photo-count).

Nevertheless, analysis by the FDA Statistician (utilizing a Fisher's exact test) showed that the mesna iv/iv/iv and iv/po/po regimens were equally effective. Though the study was small and badly flawed with respect to missing data and patient dropouts, it supports the uroprotective equivalence of iv+po mesna vs iv mesna alone.

4. Uncontrolled Studies

a) Study 007093-0019

This open, randomized, cross-over within cycle single-center study was performed to assess the urinary PK equivalence of two dosing regimens for mesna (iv only vs iv+po) administered 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 obviously under-powered and inadequately conducted study secondary to dropouts, no patient experienced above Grade I hematuria (9/13 patients evalulated). The conclusion of the Biopharmaceutics Reviewer was that the cumulative urinary excretion of the iv plus oral dosing regimen was similar to the iv reference regimen. The study supported the proposal that mesna given in the iv plus oral dosing schedule be administered iv at the time of ifosfamide infusion and po 2 and 6 hours later. The plasma PK data was felt not to be reliable secondary 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.

b) Study 07093-0016

This study was a Phase 2 trial designed to evaluate the uroprotective effect of mesna [redacted] film-coated tablets (600 mg). It was an open label, uncontrolled, multicenter

trial performed between 1992 and 1994 in a planned 188 patients with the objectives of evaluating the uroprotective effect of mesna when administered as a combination of injection solution and film-coated tablets and to assess the tolerability of that mesna regimen. No patient developed macrohematuria. There were 7 patients who developed a Grade III microhematuria and 12 patients who developed a 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 the NDA, 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 limited support for the uroprotective efficacy of oral mesna.

c) 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 [redacted] 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-acetyl-cysteine 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 provided borderline support for the efficacy of po mesna in preventing ifosfamide-induced hemorrhagic cystitis.

5. Effect on Thiol Homeostasis

[redacted] Stofer-Vogel et. al. (Br. J. Cancer 68:590-593, 1993) studied the concentrations of plasma cysteine, glutathione and their disulfides by HPLC measurement following oral or intravenous administration of mesna to eight healthy volunteers. After iv mesna administration, free cysteine rose significantly, most likely due to reduction of circulating cystine by the sulfhydryl drug (mesna). The initial rise was followed by a marked decrease of total cyst(e)ine in plasma between 30-120 minutes after mesna infusion. This was felt to be most likely due to an increased uptake of cysteine into cells and an increased urinary excretion of cyst(e)ine.

Administration of oral mesna increased circulating free cysteine to a lesser extent than intravenous mesna, and lead to a more marked increase in urinary cyst(e)ine which may contribute to uroprotection. The authors concluded that mesna depleted circulating cyst(e)ine, and may therefore markedly alter the sulfhydryl status of the cells *in vivo*, although mesna itself is not taken up by most cells. Oral mesna may be preferable to intravenous mesna in view of its effects on urinary cyst(e)ine.

Additional studies are necessary to elucidate whether these experimental findings are clinically significant. There was no data that directly addressed this concern in the studies submitted in this NDA.

VI. Recommended Regulatory Action

NDA #20-855, Mesnex^R (mesna) Tablets, submitted by ASTA Medica, Inc. on 3/25/97, contains sufficient, though limited, pharmacokinetic data in 11 cancer patients demonstrating that a mesna regimen comprised of intravenous and oral dosing is bioequivalent to the approved intravenous mesna regimen.

Literature review, as well as interim data from a controlled clinical trial conducted in the US, and a completed controlled trial from Germany lend support to the observation that the incidence of ifosfamide-induced hematuria is reduced when ifosfamide treatment is accompanied by a mesna regimen combining intravenous and oral dosing. The recommended mesna regimen is a single intravenous dose of mesna (at 20% the ifosfamide dose) administered at 0 hours, followed by [redacted] film-coated (400 mg) mesna tablets (at 40% the ifosfamide dose) administered orally at 2 and 6 hours. Evidence has been provided that demonstrates that this regimen reduces ifosfamide-induced hematuria to a similar extent as the approved intravenous mesna regimen administered at 0, 4, and 8 hours after ifosfamide (all doses at 20% the ifosfamide dose), although the findings from the controlled US study did not achieve statistical bioequivalence when the data were re-analyzed by FDA using only first cycle data, and excluding 12 patients from Center 5 (C. Julian Rosenthal), and 5 patients who discontinued from study prematurely.

[redacted]

These new findings call into question the validity of the controlled US study, which provided the urinary pharmacokinetic data upon which bioequivalence for the proposed vs the approved mesna regimens in the target population was based, as well as important safety information. Given the uncertainties currently surrounding this study, NDA #20-855, Mesnex^R (mesna) Tablets, is deemed not approvable. Upon completion of DSI's sponsor [redacted] investigation, a new controlled clinical and pharmacokinetic study comparing the proposed and approved mesna regimens may be required.

Gerald Sokol, MD Date

Julie Beitz, MD Date 3/18/98

cc:
NDA# 20-855
HFD-150/ Division File
HFD-150/ G. Sokol
HFD-150/ J. Beitz
HFD-150/ P. Guinn
HFD-860/ J. Duan

VII. Labeling Review

The following versions of product labeling and patient package insert incorporate the Medical Reviewer's comments pertinent to Mesna Tablets. These comments are located primarily in the **Clinical Pharmacology** section (last paragraph), the **Adverse Events** section (last paragraph), and the **Dosage and Administration** section, Intravenous and Oral Dosing subsection.

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