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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-763

Medical Review(s)/Statistical Review(s)

NDA 50-763: Mitozytrex

Applicant: SuperGen, Inc.

FDA Medical and Statistical Review

Medical Reviewer: Nancy S. Scher, MD

Statistical Reviewer: Mark Rothmann, PhD



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The Executive Summary of the Primary Clinical Review

1 Recommendations

1.1 Recommendations on Approvability

We recommend approval of Mitozytrex (MZ) for the indication in the innovator label of Mutamycin (Mitomycin for injection). As a 505(b)(2) application, the applicant was only required to show bioequivalence to Mutamycin. This was done by reanalysis of a double-cross over study first submitted to the NDA in 1997, but with the exclusion of 1 outlier at the time of reanalysis and utilizing statistical methodology recommended in the FDA guidance document. The analysis of a new sequential dose clinical trial showed similar pharmacokinetics and no excessive or unusual toxicity after sequential cycles of MZ.

The approved indication for Mutamycin is “for disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.” The approved single-agent dose for Mutamycin is 20 mg/m² I.V. (via a functioning catheter at intervals of 6-8 weeks). We recommend approval for MZ at the dose of 15 mg/m². Although MZ is bioequivalent to Mutamycin, it differs from the original formulation in that MZ contains the excipient hydroxypropyl-beta-cyclodextrin (HPCD). The entire human safety experience with MZ has been at the recommended 15 mg/m² dose. (See further discussion sections 6.4 and 8.)

There is no evidence that MZ is superior to existing marketed formulations of mitomycin (MMC). There is no evidence to support the claims that the addition of the excipient HPCD adds any clinical advantage over existing formulations of MMC. For the intended patient population and indication, the possible increased risk due to the excipient does not significantly impact negatively on the risk/benefit ratio compared with that of MMC.

1.2 Recommendations on Postmarketing Studies and/or Risk Management Steps as Appropriate.

The label should contain the same safety language contained in the label of the parenteral antifungal Sporonox regarding pancreatic adenocarcinoma in rats associated with HPCD, the excipient for both drugs.

Animal studies show bladder toxicity of the excipient, HPCD, when administered I.V. (Rodents were treated with 0.15 g/m² single and repeat dose, and dogs were dosed at 0.5 g/m² HPCD.) There is significant off-label use of MMC by instillation into the bladder weekly for treatment of recurrent superficial transitional cell carcinoma. Doses of up to 40 mg MMC are used weekly, which would result in intravesical exposure of up to 16 gm HPCD each week if MZ were substituted for generic MMC. The extent of systemic absorption and other safety issues have not been adequately studied for such off label use of MZ. Furthermore, unlike the advanced cancer population, these patients with superficial bladder cancer have the potential for long survival. The possible excess risk of induction of

pancreatic malignancy from HPCD is not acceptable in this population. It is hoped that inclusion of detailed animal toxicity information in the label will discourage use of MZ for intravesical therapy.

There will be not request for postmarketing commitment studies.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

This is a 505(b)(2) application that references Mutamycin (Mitomycin for injection), initially licensed to Bristol Myers Squibb in 1974. Mitozytrex (MZ) contains mitomycin (MMC), an anti-tumor antibiotic formulated with the excipient hydroxypropyl-beta-cyclodextrin (HPCD) instead of mannitol used in the innovator product. MMC is currently marketed as a generic by Bristol Myers Squibb, as well as by other companies, including SuperGen since 1998. The approved indication for MMC is “for disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.” The approved single-agent dose for MMC is 20 mg/m² I.V. (via a functioning catheter at intervals of 6-8 weeks).

SuperGen requested 505(b)(2) approval of MZ in 1997, referencing the Mutamycin label, efficacy and safety data. As a 505(b)(2) application, the applicant was only required to show bioequivalence of MZ to Mutamycin. A phase 1, double cross-over, pharmacokinetic (PK) study comparing MZ and Mutamycin in 35 patients with advanced cancer was submitted to FDA in December 1997. On 12/11/98, the Not Approvable letter from FDA to SuperGen stated that there was “unacceptable proof of bioequivalence between MZ and MMC from study ME001.” FDA recommended reanalysis of this study, as well as an additional clinical study to evaluate PK and safety of MZ in consecutive treatment cycles.

For the current resubmission, study ME001 was reanalyzed with the exclusion of 1 outlier, and bioequivalence was demonstrated between MZ and MMC. SuperGen also provided data from study ME2, a PK and safety study of 116 patients with advanced cancer who were treated with sequential cycles of MZ. The current clinical trial showed no difference in the pharmacokinetics and no excessive or unusual toxicity after sequential cycles of MZ. The study was not designed to demonstrate efficacy.

2.2 Efficacy

As a 505(b)(2) application, the applicant is permitted to rely on the efficacy and labeling of Mutamycin. There are no clinical trial data in the label of this product, which was initially approved in 1974. (See section 6.4 for further discussion.) The approved indication is “for disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.” The approved dose for Mutamycin is 20 mg/m² I.V. at intervals of 6-8 weeks.

Study ME2 is a single arm study that was not designed to demonstrate efficacy. In this PK and multiple course safety study, 116 previously treated patients with a variety of advanced cancers were received MZ at 6-week intervals. Almost all of the patients were treated with a dose of 15 mg/m² I.V. Only 4 patients in this trial received the 20 mg/m² I.V. dose specified in the Mutamycin and applicant proposed MZ labels as the single agent dose, and only 1 patient received more than a single dose of 20 mg/m². Of the 223 cycles of MZ delivered, 211, or 95% were 15 mg/m² and 218 of 223, or 98%, were 15 mg/m² or less.

The observed response rate for study ME2 (13/116 = 11.2%) is not worse than suggested in the literature for patients with advanced malignancy of diverse primary sites. The applicant reasonably concluded, "there is no evidence of diminished efficacy from the formulation" with the excipient HPCD.

2.3 Safety

MZ 15 mg/m² I.V. over 30 minutes every 6-8 weeks has an acceptable toxicity profile, similar to MMC, to which it has been shown to be bioequivalent. A safety and PK study in 116 patients with advanced cancer showed no unexpected or unusually severe toxicity with sequential cycles of MZ compared with the known toxicity of MMC. No excess renal or bladder toxicity was defined compared with MMC, which could be attributed to the HPCD excipient of MZ.

As expected for a drug with MMC as the active ingredient, the major toxicity was myelotoxicity, with neutropenia, thrombocytopenia, and anemia. No cases of HUS were identified, although this infrequent, but lethal, complication of therapy has most often been observed after cumulative doses of MMC of 50-60mg /m². No cases of idiosyncratic pulmonary toxicity or pulmonary fibrosis were identified, although the latter more commonly occurs only after longer-term therapy. (The mean number of cycles delivered in ME2 was 1.9.)

MMC is a known vesicant, extravasation of drug causing severe and progressive cellulitis, tissue necrosis and non-healing ulceration. In this study, 1 patient had "moderate" tissue necrosis at the injection site. The applicant proposed a claim that the addition of the excipient HPCD would decrease tissue toxicity compared with MMC. (See Chemistry, section 2, for discussion why this claim is unlikely on theoretical grounds.) This small single armed trial cannot be used to support this claim.

The excipient HPCD is associated with renal and bladder toxicity in animal studies and with adenocarcinomas of the pancreas. In the intended patient population and with a dosing interval of 6-8 weeks, the possible increased risk due to the excipient does not significantly impact negatively on the risk/benefit ratio compared with MMC.

2.4 Dosing, Regimen, and Administration

The prescribing instructions for the reference drug, Mutamycin (and mitomycin generics) are “at 6-8 week intervals...20 mg/m² intravenously as a single dose via a functioning intravenous catheter.” MMC and MZ have been shown to be bioequivalent and there is no evidence for altered PK with multiple cycles of MZ. However, more than 25-years of experience with MMC suggest that 20 mg/m² is an excessively toxic single agent dose, and the drug is rarely prescribed at this dose because of severe and cumulative myelotoxicity. Furthermore, there is no clinical experience or safety data for MZ with a dose higher than 15 mg/m². Of the 116 patients treated with MZ in study ME2, only 4 patients received a 20 mg/m² dose and only 1 patient received more than 1 cycle of 20 mg/m². Ninety-five per cent of the cycles of MZ delivered in study ME2 were 15 mg/m². Ninety-eight per cent were 15 mg or less. Likewise the 25 evaluable patients in study ME001 were all treated with MZ 15mg/m².

MZ should be labeled with a single agent dose of 15 mg/m² because the safety has only been evaluated at that dose level. The MMC prescribing instructions state that the dose should be “adjusted accordingly” when used in combination with other myelosuppressive agents, and this is appropriate for MZ, as well.

The label for MMC states that the drug should not be used in patients with serum creatinine greater than 1.7 mg/dl, because of 10% renal drug excretion. Since severe renal impairment prolongs the elimination rate of the MZ excipient HPCD, MZ should not be used in patients with creatinine clearance < 30 ml/min.

2.5 Drug-Drug Interactions

The label for MMC states that “acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids in patients who had previously or simultaneously received mitomycin. The onset of this acute respiratory distress occurred within minutes to hours after the vinca alkaloid injections.”

The MMC label also states that “a few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at FIO₂ concentrations greater than 50% perioperatively.”

2.6 Special Populations

Study ME2, the clinical study in the resubmission of this NDA, was not designed to demonstrate efficacy. The small number of patients in each demographic subgroup makes uncertain the clinical significance of efficacy and safety comparisons by gender, age and race.



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For study ME2, 63 (54%) of patients were male, and 53 (46%) were female. The age range was 30-82 years with a mean age of 61.1 years. The breakdown by race/ethnic group was 62 Caucasian (53%), 49 African-American (42%), 3 Asian (3%), and 2 Hispanic (2%) of the 116 treated patients.

For study ME001, analyzed for the 1997 NDA, 17 patients were male and 17 were female. The mean age was 61 years (range 38-86 years). Thirty patients were Caucasian and 4 were Hispanic.

For each safety population, older age groups and both genders were well represented. For the current study, the population was enriched in African-American representation.

The applicant provided a demographic analysis for study ME2 which showed the number of responses for patients under 65 was 8 of 65 patients (14%) and 5 of 56 patients (9%) for those older than 65, with response status unknown in 5% and 4% of these populations, respectively. By gender, for males there were 8 of 63 responders (13%) and 5 of 53 responders (9%) for females. By racial group, the number of responders for Caucasian patients was 6 of 62 (10%) and 7 of 49 patients (14%) for African-Americans. The small numbers preclude meaningful comparisons.

The applicant's safety analysis showed some differences in the frequency of adverse events between demographic groups. "Patients under age 65 had a higher incidence of fever, headache, anxiety, dizziness and coughing compared to patients 65 years and older. Males had more frequent weight loss and insomnia, and less frequent chest pain, fever, and pain compared to females. Caucasians had a higher incidence of back pain, diarrhea, peripheral edema and insomnia, and a lower incidence of headache compared to African Americans." Again, in view of the small numbers of patients in each subgroup, it is unclear if there is any clinical significance to the comparisons.

In view of 10% renal excretion of MMC and impairment of the excretion of the MZ excipient HPCD, it has been recommended that MZ not be prescribed for patients with either serum creatinine > 1.7 mg/dl or creatinine clearance < 30 ml/min. Although MMC is metabolized by the liver, there are no current guidelines for dose adjustment for hepatic dysfunction.

MZ should not be used in women who are pregnant or are breast-feeding infants.

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Clinical Review

1 Introduction and Background

1.1 Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indications(s), Dose, Regimens, Age Groups

1.1.1 Established Name: Mitomycin for Injection

1.1.2 Proposed Trade Name: Mitozytrex™

1.1.3 Drug Class: Antineoplastic antibiotic

1.1.4 Applicant: SuperGen, Inc.
4140 Dublin Blvd, Suite 200
Dublin, CA 94568
Tel: (925) 560-0100
www.supergen.com

1.1.5 Applicant's Proposed Indication

"Mitozytrex is not recommended as single-agent, primary therapy. Mitomycin has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mitozytrex is not recommended to replace appropriate surgery and/or radiotherapy."

Reviewer's comment: The proposed indication is identical, except for drug name, to the approved label for MUTAMYCIN (mitomycin for injection) revised January 2000.

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1.1.6 Dosage and Administration

The proposed "Dosage and Administration" section in the label is identical in wording to the approved label for MUTAMYCIN (except for drug name, excipient, and ml of Sterile Water for reconstitution).

"Mitozytrex should be given intravenously only, using care to avoid extravasation of the compound. If extravasation occurs, cellulitis, ulceration and slough may result.

Each vial contains mitomycin 5 mg and hydroxypropyl β cyclodextrin 2 g. To administer, add 8.5 mL of Sterile Water for Injection. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained.

After full hematological recovery (see guide to dosage adjustment) from any previous chemotherapy, the following dosage schedule may be used at 6 to 8 week intervals:

20 mg/m² intravenously as a single dose via a functioning intravenous catheter.

Because of cumulative myelosuppression, patients should be fully reevaluated after each course of Mitozytrex, and the dose reduced if the patient has experienced any toxicities. Doses greater than 20 mg/m² have not been shown to be more effective, and are more toxic than lower doses.

The following schedule is suggested as a guide to dosage adjustment:

Nadir After Prior Dose		
Leukocytes/mm ³	Platelets/mm ³	Percentage of Prior Dose to be Given
>4000	>100,000	100%
3000-3999	75,000-99,999	100%
2000-2999	25,000-74,999	70%
<2000	<25,000	50%

No repeat dosage should be given until leukocyte count has returned to 4000/mm³ and platelet count to 100,000/mm³.

When Mitozytrex is used in combination with other myelosuppressive agents, the doses should be adjusted accordingly. If the disease continues to progress after two courses of Mitozytrex, the drug should be stopped since chances of response are minimal."

1.1.7 How Supplied

Mitozytrex is supplied as 5 mg mitomycin in an amber vial, individually packaged in single cartons. Each 5 mg vial of Mitozytrex contains mitomycin 5 mg and hydroxypropyl beta cyclodextrin 2 gm.

1.2 State of Armamentarium for Indication(s)

NDA 50-763 is a 505(b)(2) application which references Mutamycin (Mitomycin for injection) first approved in 1974, for safety and efficacy. This application is for the indications approved for Mutamycin in the label revised in 1975, which are for “therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations...and as palliative treatment...”. For gastric cancer, survival is poor with available single agent and combination regimens, although some palliation may be achieved with 5-Fluorouracil (5FU), alone or in combination with doxorubicin and mitomycin (FAM regimen), or in combinations with cisplatin. Likewise, the available armamentarium for advanced pancreatic carcinoma is of limited benefit. Gemcitabine is approved for pancreatic carcinoma and shows a small survival benefit. 5-FU provides no survival benefit, but may provide some palliation, especially with radiation therapy.

The major off-label and most common usage of mitomycin (MMC) in practice is bladder instillation to prevent recurrence of superficial transitional cell carcinoma of the bladder. Another established off-label use is in combination with 5FU and irradiation as curative therapy for carcinoma of the anus.

MMC has activity in gastrointestinal, breast, head and neck, lung, bladder, and uterine cervical cancer, and is sometimes used in some salvage situations, off-label, with other drugs. (Of interest, the initial approval of Mutamycin in 1974 included, in addition to the present approved indications, squamous cancers of the head and neck, lung, and cervix, adenocarcinoma of the breast, colon, rectum and hepatic cell carcinoma and melanoma. After presentation at the Oncology Drug Advisory Committee in 1975, FDA decided to limit the indications to gastric and pancreatic carcinoma. See Section 8.4 for more information.)

The toxicity of MMC can be severe and, in some instances, unpredictable. This has contributed to the decreased frequency of utilization of this agent in recent years, particularly with the development newer, active agents and combinations for palliation of some of these cancers. Myelotoxicity due to MMC is delayed, prolonged, and cumulative. Hemolytic uremic syndrome (HUS) is a known life-threatening complication of therapy, usually observed only after cumulative doses of 50-60 mg/m². Idiosyncratic pulmonary toxicity occurs, as well as pulmonary fibrosis, the latter more common after longer-term therapy. MMC is a known vesicant, extravasation of drug causing severe and progressive cellulitis, tissue necrosis and non-healing ulceration.

1.3 Important Milestones in Product Development

Mitozytrex (MZ) was developed by SuperGen as a formulation of MMC which was theorized (but not proven) to have less cutaneous toxicity than the existing formulation, which used mannitol as the excipient. In MZ, the mannitol has been replaced by hydroxypropyl-Beta-cyclodextrin (HPCD). The addition of HPCD made the product a new drug, rather than a generic. SuperGen requested 505(b)(2)

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approval in 1997, referencing Mutamycin label, efficacy and safety data. A phase I, double cross-over, pharmacokinetic (PK) study comparing MZ and MMC was submitted to FDA in 1997 (Kozuch, P., *Cancer* 2001; 91:815-21). It failed to show bioequivalence.

- 1974 MMC approved by FDA, marketed by Bristol-Myers Squibb under NDA 50-450 as Mutamycin
- 1975 Label for MMC changed, following Oncology Drug Advisory Committee meeting; indications restricted and dose and schedule revised
- 1989 Bristol requested withdrawal of NDA (approved 1994) for business reasons (change of manufacturing site) and not for reasons of efficacy or safety. Marketed as generic Mutamycin by Bristol under AADA 62-336 since 1981; other generic MMCs have been licensed since 1995, including SuperGen (ANDA 64-144: 4/30/98)
- 02/14/96 IND [] submitted (SuperGen)
- 12/10/97 NDA 50-763 submitted under Section 505(b)
- 03/03/98 Protocol ME2 (draft) submitted under IND [] (N004)
- 09/04/98 Protocol ME2 (final) submitted (N006)
- 12/11/98 Not Approvable letter under Section 505(d) from FDA to Applicant, citing unacceptable proof of bioequivalence between MZ and MMC from study ME001 (PK double cross-over study in 35 patients). FDA stated "considerable variability in the pharmacokinetic parameters... may be explained by the substitution of mannitol with HPCD..."
- Reanalysis of study ME001 was suggested, using CDER Guidance. Additional study requested to evaluate pharmacokinetics of MZ in consecutive treatment cycles, obtaining blood samples in cycle 2 and/or 3 of treatment. This would address concerns about possible persistence of "circulating derivatives" of HPCD which "may influence the distribution and elimination of other co-administered drugs". "Alternatively, a repeat cycle toxicology study in animals to confirm that Mitozytrex does not pose a worse safety profile relative to Mutamycin could be performed."
- 03/20/02 Resubmission of NDA 50-763.
- 05/01/02 45-Day Filing. Accepted as complete response.
- 11/14/02 User fee goal date.

1.4 Other Relevant Information

Mitozytrex has not been approved in other countries.

1.5 Important Issues with Pharmacologically Related Agents

During the initial review, concern was expressed about the safety and tolerability of HPCD, which is used to improve stability and solubility of mitomycin in solution. **Sporanox** (itraconazole) injection is an antifungal solubilized by HPCD, which was approved by the FDA in 1999. (Each ml of Sporanox contains 10 mg of itraconazole and 400 mg HPCD, whereas MZ contains 2 gm HPCD per 5 mg MMC.) No unexpected toxicities from HPCD were reported for Sporanox. HPCD is an oligosaccharide which is excreted primarily by the kidneys (80-90%, Sporanox label). In subjects with severe renal impairment (creatinine clearance ≤ 19 ml/min), clearance of HPCD was decreased six-fold. For this reason, the Sporanox label advises not treating patients with creatinine clearance < 30 ml/min.

HPCD has caused pancreatic adenocarcinomas when administered orally to rats at doses from 500-5000 mg/kg/day for 25 months. This was not observed in carcinogenicity studies with mice at oral doses of 500-5000 mg/kg/day for 22-23 months. (**Sporanox** label).

2 Significant Findings From Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

2.1 Chemistry

MZ is a sterile, — powder containing MMC (5 mg) formulated with HPCD (2 g). The innovator formulation of MMC contains mannitol as the excipient. In MZ, the mannitol has been replaced by — HPCD (glucopyranose polymers, —).

The applicant asserts that MMC forms loose complexes with HPCD, resulting in a superior product because the HPCD improves MMC stability and solubility in aqueous solution and decreases injection site reactions in the event of extravasation. (See sections 4.2 and 12.1 for further discussion of injection site reactions.) The extent of complex-formation between HPCD and MMC is concentration dependent, with dissociation increasing as concentration decreases. The data provided by the applicant clearly show that there is minimal complex formation when the drug substance is reconstituted with water to a concentration of 0.5 mg/ml. There should be even less complex formation when the solution is further diluted with I.V. fluids to a concentration of 40 μ g/ml, as instructed in the label. This practical observation makes it theoretically unlikely that the addition of HPCD would have any effect on injection site reactions. The enhancement of solubilization would only occur in concentrated solutions (e.g. 20-40% HPCD). The applicant presents evidence of enhanced stability in solution (3 months vs. < 3 weeks) compared with MMC with mannitol as the excipient. However, this is clinically of little practical relevance for a product, which is marketed as — powder for reconstitution.

2.2 Animal Pharmacology and Toxicology

MZ is an antitumor antibiotic (MMC) formulated with HPCD as an excipient. MMC is an alkylating agent. MMC is carcinogenic and teratogenic in rats and mice. It is a known mutagen and clastogen and has been shown to impair fertility in mice.

HPCD is associated with an increased incidence of pancreatic adenomas and pancreatic adenocarcinomas when administered orally to rats at doses from 500-5000 mg/kg/day for 25 months. This was not observed in carcinogenicity studies with mice at oral doses of 500-5000 mg/kg/day for 22-23 months.

Single and repeat dose administration of 0.15 g/m² and 0.5 g/m² of HPCD in rodents and dogs, respectively, are associated with bladder toxicity (about 1/60th and 1/20th the amount of HPCD administered per recommended human dose of MZ on a mg/m² basis). Findings include edema, inflammation, cellular inclusions and bladder stones associated with metaplasia. Abnormalities persisted at least 3 months following dosing. Rodents also showed edema of the kidneys, as did dogs. Nephrotoxicity, including irreversible renal necrosis, observed following parenteral administration of HPCD in rodents and non-rodents, seems due to accumulation and recrystallization of HPCD in the proximal renal tubules.

The sponsor provided final reports during the last month of the review period of a repeat cycle toxicology study in dogs, comparing MZ and MMC. There were 6 dogs in each of 4 groups, with 2 dosage levels (0.2 mg/kg or 0.5 mg/kg) of each drug. The drugs were administered on days 1, 22, 42. Two dogs in the higher dosage level for each drug were either found dead or sacrificed in moribund condition on days 34 and 42 (MZ) and days 9 and 30 (MMC). This study did not provide useful information because the schedule of administration was too toxic, and the dogs appeared to have died of complications of myelotoxicity.

The applicant cites animal data to support their claim of decreased tissue toxicity at the I.V. administration site. A rat study conducted in 1992 showed decreased local tissue injury with a single intradermal injection of MZ compared with MMC. This design was not repeated, but 2 subsequent single dose I.V. rodent studies showed increase injection site ulceration for MZ compared with MMC. The recent dog study showed I.V. site chronic inflammation and fibrosis worse for MZ than MMC.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics/Pharmacodynamics

MZ is an alkylating agent (MMC) formulated with HPCD as an excipient. MMC functions as an alkylating agent, producing cross-linking of DNA. An I.V. dose is rapidly cleared by metabolism in the liver and other tissues, with 10% of a dose excreted unchanged in the urine. The per centage dose excreted in urine increases with dose.

HPCD is eliminated in the urine. Following a single I.V. dose to patients with creatinine clearance ≤ 19 ml/min, clearance was reduced six-fold compared with patients with normal renal function.

3.2 Clinical Pharmacology and Biopharmaceutics Review of NDA 50-763 Submissions

As part of the current NDA submission, the applicant provided a reanalysis of the pharmacokinetic data from Study ME001, excluding the data of 1 patient, who was felt to be an outlier. This reanalysis was evaluated by FDA Biopharmaceutics reviewers (Drs. J. Duan and Atiquer Rahman) and found to support bioequivalence between MZ and MMC. The reanalysis used 2 one-sided tests and the 1 patient (#28) was excluded from analysis. Exclusion of the outlier was reasonable because this patient had metastatic disease to liver, many co-administered drugs, and was experiencing clinical deterioration during sequential drug administration cycles.

Statistical reviewer comment: In this re-submission of the NDA, the sponsor removed one observation from the analysis for being an "outlier." When an outlier is removed from an analysis and those analyses pretend the outlier never existed, the standard errors are underestimated. Sensitivity analyses were performed using those standard errors based on all the data. In these sensitivity analyses for AUC_t , AUC_{∞} , and C_{max} , all calculated 90% confidence intervals lie within the target limits of 80%-125%. (See Appendix 3.1 for more detail.)

The current submission also included a clinical study (ME2) with pharmacokinetic data collected in consecutive cycles of therapy with MZ. Clinical sites 2, 3, 5, 9, 12, and 14 provided patients for the PK portion of the study. This study showed similar pharmacokinetic behavior during repeat cycles of therapy.

4 Description of Clinical Data and Sources

4.1 Sources of Clinical Data

NDA 50-763 contains the primary data from Study ME2, a phase 2, multicenter trial conducted in the United States from October 7, 1998, until September 8, 2000. The primary data from Study ME001, a single arm, phase 1/2 single institution study in 20 patients with refractory solid tumors, with cross-over between MMC and MZ formulations, was submitted in December 1997. The data from study ME001 were reviewed by Drs. Julie Beitz and Robert Justice and the lack of convincing demonstration of bioequivalence between MMC and MZ was the basis for non-approval of MZ in 1998. A copy of that review is attached in Appendix 3.2.

As part of the current NDA submission, the applicant provided a re-analysis of the pharmacokinetic data from Study ME001, excluding the data of one patient, who was felt to be an outlier. This re-analysis was used to support bioequivalence between MZ and MMC.

The clinical data from Study ME2 was reviewed from the paper submissions, including raw data sets and case report forms provided by the applicant. This information was provided in paper volumes 4.1, 4.2, 4.3, 4.4, 6.1, 6.2, 6.3, and 6.4.

4.2 Overview of Clinical Trials

Table 1 summarizes the clinical trials of MZ in patients with solid tumors who have previously failed chemotherapy. Only the data from study ME2 is provided at this time as new data to support resubmission of the NDA. (Original submission not approved in 1998.)

Table 1: Clinical Trials

Protocol	Enrollment Dates	Population	Treatment	#Accrued/Treated /Evaluable for PK	Endpoints
ME001	5/96-6/97	Refractory Solid Tumors	Alternating MMC/MZ 15 mg/m2 iv q6 week	35/34/25*	PK, Bioavailability, Safety
ME2	10/98-9/00	Refractory Solid Tumors	MZ 15-20 mg/m2 iv q6 week	123/116/23**	Safety, PK, Response Rate, TTP, Survival

*Patients evaluable for PK who had at least 1 cycle of both MZ and MMC

**Patients evaluable for PK who had sequential cycles of MZ

4.3 Postmarketing Experience

MZ is not currently marketed in any jurisdiction.

4.4 Literature Review

The applicant has done an adequate literature review, identifying several excellent comprehensive reviews of MMC and referencing several articles which discuss the special toxicities of MMC. The Medical Reviewer searched PDQ for disease-oriented state-of-the-science chemotherapy recommendations and PubMed, using search terms linking Mitomycin and Clinical Trials. There was very limited information in the literature to allow isolation of MMC treatment effect and randomized trials identified by the medical reviewer were small.

5 Clinical Review Methods

5.1 Describe How Review was Conducted

A single phase 2 trial (ME2), conducted in the United States from October 7, 1998, until September 8, 2000, is the basis for the current resubmission. The clinical data from Study ME2 was reviewed from the paper submissions, including raw data sets and case report forms provided by the applicant. This information was provided in paper volumes 4.1, 4.2, 4.3, 4.4, 6.1, 6.2, 6.3, and 6.4. Summary data and previous analyses of Study ME001, submitted in 1998, were also reviewed. A copy of the 1998 NDA Medical Review by Drs. Beitz and Justice is attached in Appendix 3.2.

5.2 Overview of Materials Consulted in Review

The following materials were reviewed by the medical officer:

- The regulatory history of the application
- The 1998 reviews related to the initial NDA submission

- IND #
- Correspondence between the Applicant and FDA in Division Files
- Original submission of protocol ME2 and amendments
- Paper submissions of the NDA, including raw data sets and case report forms for protocol ME2, and re-analysis of study ME001
- Electronic labeling proposal
- Relevant published literature
- Study report and Medical Officer Review for NDA 50-450, Mutamycin, 1972
- Mitomycin C labels from 1974 to present

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

CDER's Division of Scientific Investigations (DSI) conducted an audit of 2 of 13 clinical centers participating in study ME2. Centers with larger accruals were chosen to assess data quality and integrity. These sites treated half of the 116 patients who received the study drug.

DSI was concerned about the quality of the data at 1 of the sites. (See below "Protocol Violations".)

5.4 Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were conducted in accordance with accepted ethical standards. Protocol ME2, its amendments and patient informed consent were reviewed by an Institutional Review Board (IRB) that complies with the requirements set forth in 21CFR Part 56 of FDA regulations. Written informed consent was required before enrolling a patient in the trial. The applicant asserts that the study was performed according to the principles of Good Clinical Practices (GCPs) and in accordance with the Declaration of Helsinki. The DSI investigator had some concerns about procedures at one investigational site. (See below "Protocol Violations".)

5.5 Evaluation of Financial Disclosure

The applicant has provided FDA form 3454 for clinical study ME2 and asserted that the investigators have no financial interest.

6 Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

Study ME2 is a single-armed study that was not designed to demonstrate efficacy and the conduct of the trial at one site raises concerns about the reliability of the response rate data which was recorded. However, the overall response rate observed in the study is similar whether this site is included ($13/116 = 11.2\%$) or excluded from the analysis ($10/86 = 11.6\%$). The applicant reasonably concluded that "there is no evidence of diminished efficacy from the formulation" with the excipient HPCD.

As a 505(b)(2) application, the applicant is permitted to rely on the FDA's prior review and findings of efficacy and the labeling of the innovator product, Mutamycin. There are no

clinical trial data in the label of this Mutamycin which was initially approved in 1974. (See section 6.4 for further discussion.) The observed response rate in study ME2 is not worse than suggested in the literature for patients with advanced malignancy of diverse primary sites. Only 4 patients in this trial received the 20 mg/m² I.V. dose specified in the Mutamycin and proposed MZ labels (as the single agent dose), and only 1 patient received more than a single dose of 20 mg/m². Of the 223 cycles of MZ delivered, 211, or 95% were for 15 mg/m² and 218 of 223, or 98%, were for a dose of 15 mg/m² or less.

6.2 General Approach to Review of the Efficacy of the Drug

The efficacy database consists primarily of a single arm, phase 2 trial (ME2) of successive cycles of Mitozytrex in patients with solid tumors who failed previous chemotherapy. The study was designed to show "pharmacokinetic equivalence between repeated cycles" of MZ. A reanalysis by the applicant of study ME001, the subject of the original December 1997 NDA submission and 1998 reviews, is provided to support bioequivalence of MZ and MMC, to permit reference to efficacy and toxicity of Mutamycin in this application.

6.3 Detailed Review of Trials by Indication

Clinical Study ME2, entitled "Study of the Tolerance and Efficacy of Mitozytrex in Patients with Solid Tumors Who Have Failed Previous Therapy."

Conducted: October 7, 1998-September 8, 2000

A list of the participating investigators and institutions appears in Appendix 3.3.

6.3.1 Protocol Review

Synopsis/Study Design

Protocol ME2 was a multicenter (13 sites in U.S.), single arm, phase 2 trial in adult patients with solid tumors who have failed previous therapy. Patients were to be treated with MZ 15-20 mg/m² I.V. every 6 weeks. The plan was to treat patients with 3 courses of MZ in the absence of progressive tumor, irreversible severe or life-threatening toxicity. Patients could be continued for additional cycles, but not exceed a maximum cumulative dose of 60 mg/m². The primary endpoint was safety of MZ. Response rates were determined. Pharmacokinetics of MZ were to be evaluated during consecutive cycles of therapy (2 and 3), to address FDA concerns about cumulative or unexpected toxicity with successive cycles. The initial plan was to treat 20 patients, 14 fully evaluable. Fully evaluable patients were to have received at least 3 courses of study drug. The applicant enrolled 123 patients, of whom 116 had at least one course of therapy. Pharmacokinetic data were evaluable for 23 patients completing cycles 1 and 2 and 10 patients completing cycles 1 and 3. Not all patients who completed multiple cycles of therapy had blood drawn for PK.

Objectives

Primary:

- To test the possibility of $\geq 20\%$ incidence of unexpected or unexpectedly severe toxicity

Secondary:

- To evaluate tolerability and tumor response patterns
- To compare pharmacokinetic parameters after successive treatment cycles

Inclusion Criteria

- Age \geq 18 years
- Histologic proof of malignant solid tumor
- Refractory to chemotherapy and not candidates for higher efficacy therapy
- Estimated life expectancy \geq 16 weeks
- Performance status \leq 2
- No chemotherapy or radiation for 3 weeks (6 weeks for nitrosoureas)
- ANC \geq $1.5 \times 10^9/l$ and platelets \geq $100 \times 10^9/l$
- SGPT, SGOT and alkaline phosphatase \leq 2x upper limit of normal
- Bilirubin \leq 1.5 mg%
- Serum creatinine \leq 1.7 mg%
- Written informed consent

Exclusion Criteria

- Pregnant or lactating women
- Women of childbearing potential, not using approved birth control method
- Central nervous system metastases
- Prior therapy with mitomycin
- Concomitant radiation therapy or other chemotherapy anticipated
- Addiction or psychiatric disease expected to interfere with follow-up
- Active gastric or duodenal ulcers or other bleeding source
- Serious active infection or intercurrent illness

Treatment

Patients were to receive 15-20 mg/m² of MZ I.V. every 6 weeks for 3 cycles. Patients could receive a fourth cycle if the total cumulative dose was not more than 60 mg/m². Treatment was to be given by infusion into an intravenous catheter over 30 minutes. The drug was supplied as mitomycin 5 mg and HPCD 2 gm in a vial, to be reconstituted with 8.5 ml of sterile water.

Reviewer's comment: There is no clear guidance in the protocol as to how the first dose should be chosen (15 or 20 mg/m²).

Dose adjustments for each subsequent course were to be based on the "nadir neutrophil and platelet counts determined by weekly blood counts, the presence of febrile neutropenia and the duration of neutropenia." The dose for a course was to be decreased to 75% of the preceding course if nadir counts were $< 0.5 \times 10^9/l$ for neutrophils or $< 25 \times 10^9/l$ for

platelets, or for febrile neutropenia, or if treatment had to be postponed > 2 weeks for low blood counts.

The minimal blood counts to resume treatment were absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/l$ and platelets $\geq 100 \times 10^9/l$. If patients did not recover from toxicity by the time the next course was due, weekly assessments were to be done. Patients were taken off study if they did not recover within 3 weeks from the date a course was due.

Concomitant Medications

No concomitant chemotherapy and no radiation therapy were permitted. Use of other medications during the study was to be kept to a minimum and documented in the case report form (CRF).

Schedule of Assessments

Baseline assessments include history, physical, performance status (PS), vital signs (VS), weight, height, tumor staging, pregnancy test, CBC, platelets, PT/PTT, serum chemistry, urinalysis (UA), Chest X-ray, EKG. Baseline assessments should be done within 1 week before starting treatment, except imaging studies and EKG may be done within 30 days before starting therapy. Weekly assessments while on-study include history, injection site examination with physical as indicated, PS, VS, CBC, platelets. Serum chemistry and UA were to be done at the start of each course. Tumor restaging and response evaluation, PT/PTT, and Chest X-ray were to be done every 2 courses. At the end of study, assessments were to include history, physical, PS, VS, weight, CBC, platelets, PT/PTT, serum chemistry, UA, Chest x-ray and EKG. Patients were to be followed post-study until death.

Pharmacokinetic Assessments

The protocol specified that blood levels of mitomycin before and at times after MZ infusion would be determined for a minimal sample of 12 patients receiving multiple cycles of MZ, in order to make inpatient comparisons for successive cycles of therapy. The parameters to be compared were area under the curve (AUC), area under the first moment curve (AUMC), concentration at time 0 (C_0), maximum observed concentration (C_{max}), total body clearance (Cl_{tot}), steady-state volume of distribution (V_{dss}), elimination half-life ($t_{1/2\lambda}$).

The time intervals after the end of infusion of each dose of study drug are 5, 10, 15, 30 minutes and 1, 2, 4, and 6 hours.

Efficacy Criteria and Study Endpoints

All patients who received study medication were to be included in the safety analyses. Toxicity was to be graded by the National Cancer Institute Common Toxicity Criteria (NCI CTC). Adverse Events (AEs) were to be analyzed by overall incidence and by body system, intensity, and course of treatment. Serious AEs (SAEs), those requiring hospitalization, considered life threatening or fatal were to be summarized. Response rate (RR), Time to

Progression (TTP), and survival times were calculated for patients with measurable or evaluable indicator lesions.

Tumor Response Criteria:

A lesion was considered measurable if it could be “measured in its 2 major diameters on the same plane.” A lesion was considered evaluable if it was measurable in only 1 diameter or could be viewed, as through an endoscope. “Except for brain lesions, tumors must have an initial largest diameter of 2.5 cm or greater.” Complete Response (CR) is complete disappearance of all lesions, signs and symptoms of disease maintained for ≥ 1 month. Partial Response (PR) is defined as “diminution by more than 50% of the measurements in the absence of any new or progressing lesions” lasting 1 month. “Measurements” are defined as “the sum of the product of the largest diameters, on the same plane, of all measurable lesions, and of the measured diameter of all measurable lesions.” Stable Disease (SD) is change of $< 10\%$. Progressive Disease (PD) is appearance of any new lesion or increase of existing lesions by 25% or more.

Time to Event Endpoints:

- TTP is “the time from start of treatment or randomization” until first documentation of progression, or until last date patient was known to be in remission.
- Remission duration is “evaluated from the first documentation of response...until first documentation of progress or last date patient was known to be in remission.”
- Disease-Free Survival (DFS) or Progression-Free Survival (PFS) is defined “from the start of treatment or from randomization until the first documentation of relapse, ...or until the last date the patient was known to be in remission.”
- Survival is defined as “time from the start of treatment or from randomization until the date of death or until the last date ...known to be alive.”

Reviewer comment: The definition of time to event endpoints is usually from the date of study entry. If patients were lost to follow-up, data should be censored from that time. Time to event analyses are uninterpretable in the context of a single arm trial.

Pharmacokinetic Endpoints:

- AUC
- AUMC
- C_0
- C_{max}
- Cl_{tot}
- V_{dss}
- $T_{1/2lambda}$

Statistical Considerations/Sample Size



In evaluating the safety and tolerability of MZ, the primary objective was to evaluate the incidence of toxicity that was “unexpected, unexpectedly severe, or rare” compared with known toxicities of MMC. According to Gehan’s formula, it was expected that if 14 evaluable patients were recruited to the trial, “the probability that none of them will present with an unexpected event was less than 5% (...0.044) if the true frequency of unexpected events in the general patient population is 20% or higher. It was prespecified that it might be necessary to increase the sample size “if less than 12 of the initially recruited patients were unable or unwilling to undergo blood sampling for kinetics.”

Protocol Amendments/Changes

Although no formal amendments were reported to the protocol, the number of Principal Investigators (PIs) was expanded from 1 (John McDonald, M.D., St. Vincent’s Hospital, New York) to a total of 13 at multiple U.S. sites. (See Appendix 3.3.) This expansion occurred as the number of patients was dramatically increased. The initial estimate was that 20 patients would be entered into the trial to ensure the recruitment of 14 evaluable patients, patients who would complete 3 sequential cycles of chemotherapy with MZ and be available for pharmacokinetic testing. Ultimately, 123 patients were recruited and 116 patients were treated to obtain an adequate number of patients for PK analysis. There were 13 patients evaluable for PK in cycles 1 and 2; 10 patients were evaluable for PK in cycles 1 and 3. (See Table 2.)

6.3.2 Trial Results

STUDY ME2

6.3.2.1 Enrollment, Patient Disposition, Demographics, Baseline Characteristics

Enrollment and Disposition

A total of 123 patients were enrolled at 13 U.S. sites. The sites and number of patients treated at each site are listed in Appendix 3.3. (Table 12 also lists the number of patients treated per site, number of SAE and tumor responses per site.)

One hundred sixteen patients received at least one cycle of MZ and 69 patients were treated with 2 to 4 cycles of study drug, for a total of 223 treatment courses from October 1998 until September 2000. The following reviewer table lists the total number of treatment cycles completed by study patients (from summary data in the study report, Section 4.2, and verified against individual patient treatment data in Appendix 3, Listing 5). The applicant included all patients treated with at least one cycle of study medication in the analysis for safety and efficacy.

Table 2: Total Number of Treatment Cycles Completed Per Patient

Number of Cycles	Number of Patients	Per Cent of Treated Patients
0	7	-
1	47	41
2	39	34
3	22	19
4	8	7
TOTAL	123	-

The following applicant table describes the patient disposition during the study:

Table 3: Patient Disposition

Disposition	N	%
All Patients Treated in the Study	116	
Number of Treatment Courses Completed:		
1 or more	116	100
2 or more	69	59
3 or more	30	26
4	8	7
Reason for Discontinuation (All treated patients):		
Disease Progression	75	65
Completed Treatment	20	17
Study Drug Toxicity	6	5
Symptomatic Progression	3	3
Patient Request	3	3
Death	5*	4
Other	4	3
Number of Days on the Study:		
Mean	74.2	
Standard Deviation	39.2	
Median	66	
Range	8-165	

Source: TABLE 6, Appendix 2
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Reviewer comment:

***This number is misleading and does not include an additional 3 patients who died within 30 days of the last dose of drug. This clarification was obtained after requesting additional information from the applicant about inconsistencies in numbers of deaths in the study report. (See Reviewer comment, top of page 35, for further details.)**

The range of days on study was 8-165 days and the mean number of days on study was 74.2.

The median days on study was 66, just slightly longer than the duration of the 42-day treatment cycle. Disease progression was reported as the reason for discontinuation from study for 65% of patients.

Baseline Demographic and Disease Factors

Gender, age, and body size are described in the following applicant's table from the study report.

Table 4: Gender, Age and Body Size

Sex	
Male	63(54)
Female	53(46)
Age (years)	
Range	30-82
Mean	61.1
SD	12.55
Height (cm)	
Range	136-191
Mean	169.9
SD	9.62
Weight (kg)	
Range	36-141
Mean	76.0
SD	18.77
Body Surface Area (m)	
Range	—
Mean	1.9
SD	0.24

Source: TABLES 1. 1 and 2, Appendix 2..

There were 63 males and 53 females. The mean age was 61.1 years. The following reviewer's table displays demographic data regarding race of the participants:

Table 5: Racial Distribution of the Study Patients

Race	# of Patients (%)
Caucasian	62 (53)
African-American	49 (42)
Asian	3 (3)
Hispanic	2 (2)

The following applicant's table provides information on performance status, stage and histology of the participants.

Table 6: Performance Status and Histology of Study Patients

(Population: All Treated Patients) (N=116)

Performance Status	N (%)
0	29(25)
1	60(52)
2	22(19)
3	2(2)
Unknown	3(3)
Stage	
I	1(1)
II	2(2)
IIA	1(1)
III	1(1)
IIIB	2(2)
IV	107(92)
IVA	1(1)
Histology	
Adenocarcinoma	74(64)
Infiltrating ductal (not otherwise described)	10(9)
Squamous cell	9(8)
Non-small cell	6(5)
Clear cell	2(2)
Other (see text)	12(11)
Unknown	3(3)

Source: TABLE 1. 1, Appendix 2.

Almost all patients had metastatic cancer (92% "stage IV"), with 64% categorized as adenocarcinoma. More than three quarters of the patients had good baseline performance status, with 25% of patients ECOG PS 0 and 52% ECOG PS 1. The following reviewer table lists the incidence of cancer primary sites, from individual patient diagnoses provided in the study report, Appendix 3, Listing 1.

Table 7: Cancer Primary Sites of Study Patients

Primary Site	Number of Patients	Per Cent of Treated Patients
Colon	32	28
Breast	15	13
Lung	15	13
Prostate	12	10
Rectum	7	6
Gastric	5	4



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Primary Site	Number of Patients	Per Cent of Treated Patients
Head and neck	5	4
Liver	4	3
Esophagus	3	3
Other *	18	16
TOTAL	116	100

* Other includes 1 or 2 patients each with primary of bladder, cervix, kidney, ovary, thyroid, melanoma, mesothelioma, leiomyosarcoma, unknown primary, Kaposi's sarcoma.

Previous Treatment

The following reviewer table is from summary data in applicant's Table 4, Appendix 2.

Table 8: Previous Treatment for Malignancy

Treatment	# (%)	1 Regimen	2 Regimens	≥ 3 Regimens
Chemotherapy	109 (94)*	28 (24)	39 (34)	42 (36)
Radiotherapy	67 (58)	-	-	-
Surgery	102 (88)	-	-	-

Reviewer's comment: /

**Previous treatment with chemotherapy was an entry criterion that was not met by 7 patients per applicant's tally, 8 patients per reviewer's tally. (See "Protocol Violations".)*

The applicant granted waivers to all these chemotherapy naive patients, except for 2 patients who were treated but for whom no waiver was requested by the investigators. One of these patients had recurrent floor of the mouth cancer and one had gastric adenocarcinoma. The patients who were granted waivers included 2 additional patients with gastric adenocarcinoma, 1 with esophageal carcinoma, and 3 with hormone-refractory prostate cancer (AIPC). Although these were significant protocol violations, none of these patients were deprived of potentially curative therapy.

Study Treatment

The protocol specified that patients were to be treated with study drug 15-20 mg/m² I.V. every 6 weeks. The following reviewer table lists the distribution of doses of study drug per treatment cycle. (Data obtained from Appendix 3, Listing 5.)

Table 9: Dose of Study Drug Per Patient Each Treatment Cycle

	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Dose Mg/M ²	# of Patients	# of Patients	# of Patients	# of Patients
10-13	2	2	2	1
15	114	63	27	7
20	0	4	1	0
TOTAL Patients	116	69	30	8

Of the 223 cycles of MZ delivered, 211 of these treatments, or 95 % were 15 mg/m². Only 7 of 223 cycles or 3% of treatments were a lower dose of 10-13 mg/m² (5 patients), while 4 patients received the higher 20 mg/m² dose for a total of 5 of 223 or 2% of treatment cycles.

Reviewer comment: Although the protocol was imprecise in specifying the starting dose, the actual variation in dosage was minor. Ninety-eight per cent of the treatments in study ME2 were 15 mg/m² or less. The 25 evaluable patients in study ME001 were also treated with MZ dosage of 15 mg/m². The recommended single agent dosage in the MMC label is 20 mg/m² I.V. q6-8 weeks, which is the applicant-proposed dosage in the proposed label for MZ. This is too high, because there is no clinical experience or safety data for MZ above 15 mg/m².

Protocol Violations

The following reviewer's table lists violations at all sites that were identified by the applicant and violations identified by FDA audit of one site.

Table 10: Protocol Violations All Sites and a Single Audit Site

Violation	All Sites Including Audit Site (Applicant Reported) # Patients	Single Audit Site Only (FDA Reported) # Patients
Inclusion/Exclusion Criteria		
No prior chemotherapy	8	6
No prior chemotherapy, AIPC*	3	3
Baseline laboratory values	8	5
Off prior chemotherapy < 3 weeks	1	2
Concurrent hormone therapy	Not mentioned	7
No measurable disease	Not mentioned	11
Treated past progression	6	5

*AIPC = Androgen independent prostate cancer; these patients are subset of row above

Reviewer comment: The DSI audit identified 24 additional patients with protocol violations, who were not reported by the applicant.

There were 5 patients at an audited site who did not meet laboratory eligibility requirements due to elevated alkaline phosphatase values, most in patients with bone metastases. However, the applicant's summary identified only 2 patients at site 8 with unacceptable baseline laboratory studies (1 alkaline phosphatase, 1 SGOT). The applicant identifies an additional 6 patients at other sites who did not meet laboratory eligibility requirements, but were given waivers, including 3 patients with thrombocytopenia. If one includes distinct patients from the applicant analysis and from the FDA site audit, the total number with baseline laboratory studies deviant from protocol specifications is 12.

For the categories of violations other than "baseline laboratory values", the FDA (DSI) site audit identified no new patients in the "no prior chemotherapy" category, in general, or for patients with AIPC. The audit identified 1 patient not previously identified in the category of "off prior chemotherapy < 3 weeks" and 2 unique patients who were "treated past

progression". All 7 patients listed with "concurrent hormone therapy" and all 11 patients with "no measurable disease" were identified only by FDA site audit.

The 8 patients who did not meet entry criteria because they had no prior chemotherapy included 3 patients with gastric adenocarcinoma, 1 with esophageal carcinoma, 1 with recurrent floor of mouth cancer, and 3 with androgen independent prostate cancer (AIPC). As discussed previously, although the protocol was violated, none of these patients was deprived of potentially curative therapy.

Regarding concurrent hormone therapy, although not allowed in the protocol, it seems medically appropriate for many of the patients with prostate cancer who have not undergone orchiectomy to continue androgen-deprivation therapy.

The large number of patients without measurable disease noted by FDA at the audit site, but not identified by the applicant, is difficult to reconcile. For this study, which is largely a safety and pharmacokinetics study, not designed to show efficacy, the protocol could have been written to include patients with and without measurable disease. However, the inability of some of the investigators to follow the protocol and/ or the applicant to identify deviations, may reflect on the conduct of all aspects of the study.

Many of the violations discussed up to this point could have been better addressed by amending the protocol formally, rather than granting numerous waivers.

The applicant reported 6 patients in the entire study who were either treated "despite evidence of disease progression or ambiguous or conflicting evidence of stable disease that needed clarification." FDA identified 5 such patients, including an additional 2 patients not reported by the applicant. This practice of treating patients with progressive disease raises questions about study conduct at the site and makes efficacy data from the site suspect. Although safety and pharmacokinetic data should not be affected, this kind of violation also raises concerns about how closely the trial was monitored by the applicant.

6.3.2.2 Efficacy Results

Efficacy Results – Sponsor’s Assessment

All patients treated with any study drug were included in the analyses. The primary efficacy criterion was tumor response rate. TTP and median survival were determined. The following applicant’s table summarizes the investigator-reported best tumor responses.

Table 11: Tumor Response

Treatment Response	Number (%)
Complete response	1 (1)
Partial response	12(10)
Stable disease	40(34)
Disease progression	57(49)
Unknown	5(4)
Early death	1 (1)

The applicant states that “all data were monitored and verified against source documents on an ongoing basis at the study sites.”

Reviewer comment: As noted above (Protocol Violations), the data, at least in some circumstances, seem not to have been closely monitored by the applicant. Although the above table lists a response, or lack thereof for each of the treated 116 patients, the applicant does not discuss the possible unreliability of some of these data in light of protocol violations.

The total number of responses is 13 of 116 patients treated (11.2%), which is similar to literature reports of single agent efficacy of MMC in a mixed population of previously treated patients. The greatest number of responses (3) was noted at each of the 2 larger sites.

The following reviewer table shows the incidence of responses (and SAEs) by treatment site.

Table 12: Incidence of Responses and SAEs by Treatment Site

SITE #	# TREATED	# SAE	# RESPONSES	COMMENT
1	5	1	0	
2	3	1	0	
3	6	0	1	PR
4	6	3	0	
5	8	4	1	PR
6	1	0	0	
7	8	5	1	PR
8	30	8	3	2 PR, 1 CR
9	9	4	4	PR
11	28	1	3	PR
12	2	0	0	
13	9	0	0	
14	1	0	0	
TOTAL*	116	27	13	12 PR, 1CR

*There was no site 10

Reviewer comment: In an exploratory analysis, if the data from the audited site are excluded from the analysis of response rate, there are 10 responses in 86 patients treated or 11.6%. This is similar to the overall response rate for the entire cohort (11.2%) and compares favorably to the literature for an unselected group of patients with advanced cancer.

The applicant reports the median time to disease progression for *all* patients was 2.7 months and the median survival time was 5.5 months.

Reviewer comment: Both TTP and survival were defined imprecisely as “the time from start of treatment or randomization” with TTP continuing until “first documentation of

progression, or until last date patient was known to be in remission". Time to event analysis is not interpretable in a small, single arm trial.

The applicant reasonably concludes that "there is no evidence of diminished efficacy from the formulation" with the excipient HPCD.

6.4 Efficacy Conclusions

Study ME2 is a single arm study that was not designed to show efficacy and the conduct of the trial at one site raises concerns about the reliability of the response rate data. However, the response rate is similar whether the suspect site is included (13/116 = 11.2%) or excluded from the analysis (10/86 = 11.6%). The applicant reasonably concluded, "there is no evidence of diminished efficacy from the formulation" with the excipient HPCD.

As a 505(b)(2) application, the applicant is permitted to rely on the efficacy data that was the basis of approval and labeling of Mutamycin. There are no clinical trial data in the label of this product which was initially approved in 1974. We reviewed the Medical Reviewer's Summary and clinical data from the original Mutamycin NDA. In NDA 50-450, there were 1249 evaluable case reports of patients with solid tumors of a large variety of different sites. The Mutamycin Reviewer stated, "There are 187 cases or 15% objective responders. However, this is achieved by using a 25% improvement rate for 2 weeks. If this factor is left out and only responses of 50% or more for 1 month or more are counted then the overall response rate drops to 7%." He further observes, referring to the 25%/2 week criteria, that "the most favorably responding tumors were carcinoma of breast 25%, squamous carcinoma of the cervix 24%, squamous cell ca mixed sites 23%, and Adeno-Ca of Other Sites 21.5%." Although lack of measurable disease did not permit determination of objective response, a group of 38 patients with gastric carcinoma were felt to have had sufficient subjective improvement that they seemed to benefit "for a longer duration than the average 'objective' response". There was a 10% response rate among the 214 patients with gastric cancer, a 14% response for the 90 patients with pancreatic carcinoma. (It should be noted that current tumor response criteria require a 50% reduction in volume sustained for at least 1 month.)

In 1975 the Oncology Drug Advisory Committee retrospectively reviewed the NDA. There was concern because of lack of consistency in drug doses and regimens in the NDA study population and the broad approval, including indications for cancer of the head and neck, lung, breast, cervix, colon, liver, and melanoma, as well as gastric and pancreatic. Subsequent to that meeting the label was rewritten to exclude all indications except gastric and pancreatic cancer. The original dosage was Mutamycin 0.05 mg/kg/day daily x 10 with a 2 day rest between the fifth and sixth days, with "repeat in 2 to 3 weeks if no bone marrow toxicity occurs." Subsequently, in 1975, this ill-advised dose was changed to 20 mg/m² at intervals of 6 to 8 weeks.

The indication in the MMC and proposed Mitozytrex labels is "not recommended as single-agent, primary therapy...useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations...and as palliative treatment when other modalities have failed." There is no mention of the most significant (off-label) modern usage, where the drug is used with potentially curative intent, in combination therapy for

squamous carcinoma of the anus, and as intravesical therapy for superficial bladder cancer. (For anal cancer, MMC is administered with 5FU and irradiation, with the MMC dose of 10 mg/m² I.V. on days 1 and 29 only or 15 mg/m² day 1 only.) These indications will not be included in the label for MZ because, as a 505(b)(2) application, MZ is limited to the efficacy and indications in the label of the innovator product.

It is very difficult to isolate single-agent efficacy of MMC from the literature as it was most frequently studied in combination, in regimens that were developed empirically. The limited number of randomized trials available for review, employ small numbers of patients.

7 Integrated Review of Safety

7.1 Brief Statement of Findings

MZ 15 mg/m² I.V. over 30 minutes every 6-8 weeks has an acceptable toxicity profile, similar to MMC, to which it has been shown to be bioequivalent. A safety and PK study in 116 patients with advanced cancer showed no unexpected or unusually severe toxicity with sequential cycles of MZ compared with the known toxicity of MMC. No excess renal or bladder toxicity, which could be attributed to the HPCD excipient of MZ, was defined compared with MMC.

As expected, the major toxicity was myelotoxicity, with neutropenia, thrombocytopenia, and anemia. No cases of HUS were identified, although this infrequent, but lethal, complication of therapy has most often been observed after cumulative doses of MMC of 50-60mg /m². No cases of idiosyncratic pulmonary toxicity or pulmonary fibrosis were identified, although the latter more commonly occurs only after cumulative doses of MMC of 50-60mg /m², as well.

MMC is a known vesicant, extravasation of drug causing severe and progressive cellulitis, tissue necrosis and non-healing ulceration. In this study, 1 patient had "moderate" tissue necrosis at the injection site. The applicant proposed a claim that the addition of the excipient HPCD would decrease tissue toxicity compared with MMC. (See Chemistry, section 2, for discussion why this claim is unlikely on theoretical grounds.) The study cannot be used to support the claim based on 1 small single armed trial.

Reviewer audit of laboratory data and CRFs did not discover any unreported cases of HUS, study drug related urinary toxicity or definite unreported treatment related deaths.

7.2 Materials Utilized in the Review

The following materials were reviewed by the medical officer:

- The regulatory history of the application
- The 1998 reviews related to the initial NDA submission
- IND [redacted]
- Correspondence between the Applicant and FDA in Division Files
- Original submission of protocol ME2 and amendments

- Paper submissions of the NDA, including raw data sets and case report forms for protocol ME2, and re-analysis of study ME001
- Electronic labeling proposal
- Relevant published literature
- Study report and Medical Officer Review for NDA 50-450, Mitomycin C, 1972-74
- Mitomycin labels from 1974 to present

7.3 Description of Patient Exposure

In study ME2, 116 patients were treated with a least one cycle of MZ and 69 patients were treated with 2 to 4 cycles of study drug at approximately 6 week intervals, for a total of 224 treatment courses from October 1998 until September 2000. See section 8.3.2.1 for tables and details of exposure. Table 2 lists the number of treatment cycles completed by study patients. Tables 3 and 4 provide demographic data. Table 9 lists the dose of study drug delivered per patient in each treatment cycle. The range of days on study was 8-165 days and the mean number of days on study was 74.2 (standard deviation=39.2).

7.4 Safety Findings from Clinical Studies

Applicant assessment and analysis of safety

Adverse events (AE), serious adverse events (SAE), and laboratory studies were the main safety variables. At the end of the study, patients were to be assessed 6 weeks following their last treatment. There was also provision in the protocol for the following information to be collected quarterly for the first year and yearly thereafter for all patients following study end: Further treatment and adverse reactions; Tumor history, relapse/progression and second tumor status; Survival status. All patients who received at least 1 dose of study medication were included in the safety analysis.

AEs were coded by the COSTART system (Coding Symbols for Thesaurus of Adverse Reaction Terms). The incidence was determined for AEs, defined as "any unintended event (clinical sign or symptom) observed or reported for the first time after the administration of study medication, whether attributed to study medication or not." Data tables were generated to summarize:

- Number of patients with any AE, classified by body system
- Number of patients reporting AEs by intensity (mild, moderate, severe, fatal)
- Number of patients reporting AEs by treatment course.

SAEs were defined as AEs "requiring or prolonging hospitalization, considered life threatening, or leading to fatalities." CRFs were provided for those patients experiencing SAEs.

Reviewer comment: The protocol states that AEs were to be graded by NCI Common Toxicity Criteria, but the AEs are actually classified as 1=mild, 2=moderate, 3=severe, 4= life-threatening, 5=fatal.

Overall incidence and severity of adverse events

Of the 116 treated patients, all but one reported 1 or more AEs, and 10% or more patients reported 22 AEs. AEs reported by 15% or more patients include [N (%): Asthenia 52 (44.8%), nausea 43 (37.1%), anemia 32 (27.6%), abdominal pain 20 (17.2%), pain 33 (28.5%), anorexia 29 (25%), dyspnea 23 (19.8%), constipation 20 (17.2%), vomiting 30 (25.9%), leukopenia 30 (25.9%), peripheral edema 19 (16.4%), thrombocytopenia 27 (23.3%), diarrhea 18 (15.5%). Only 1 patient was reported to have injection site pain or reaction; a 79 year-old man with prostate cancer was noted to have “moderate skin necrosis” 60 days after the last dose.

Life threatening or lethal adverse events

The following reviewer table lists life threatening (intensity 4) and lethal (intensity 5) AEs organized by body system. (Derived by reviewer from applicant Table 9 in study report.)

Table 13: Life Threatening and Lethal Adverse Events by Body System

Body System	Adverse Event	Life Threatening # of Patients (%)	Lethal # of Patients (%)
Body as a whole	Ascites		1 (0.9)
	Pain	2 (1.7)	
Cardiovascular	Cerebrovascular accident		1 (0.9)
	Cardiac arrest		1 (0.9)
	Hemorrhage		1 (0.9)
Digestive	Liver carcinoma		1 (0.9)
Hemic & Lymphatic	Leukopenia	2 (1.7)	
	Thrombocytopenia	5 (4.3)	
Metabolic, Nutritional	Hyperkalemia	1 (0.9)	
	Peripheral edema		1 (0.9)
Nervous	Coma	1(0.9)	
	Peripheral neuritis	1 (0.9)	
Respiratory	Pneumonia		1 (0.9)
Skin, Appendages	Skin melanoma		1 (0.9)
Urogenital	Kidney failure		1 (0.9)

Nine patients had lethal AEs (intensity 5). The applicant stated in the study report that the reasons for discontinuation from the study (See Table 3) included death for 5 patients, study drug toxicity for 6 patients. The applicant states that none of the lethal AEs were considered related to study medication.

Reviewer comment: Although there seems to be a discrepancy between the applicant's listing of 9 patients dead on study but only 5 patients discontinuing therapy because of death, apparently the decision not to continue therapy because of early disease progression was made in several patients before they died within the 30 day period. It seems likely that,

among the life-threatening AEs, leukopenia (2 patients) and thrombocytopenia (5 patients) were therapy related.

Severe (Intensity 3) Adverse Events

There were 24 severe (intensity 3) AEs recorded for more than 1 patient. The AEs and the number of patients reported by the applicant include: asthenia (10); anemia (8); leukopenia (8); thrombocytopenia (8); dyspnea (6); pain (6); abdominal pain (6); constipation (5); nausea (5); dehydration (5); anorexia (4); vomiting (4); back pain (3); fever (3); headache (3); hypovolemia (3); respiratory disorder (3); urinary tract disorder (3); diarrhea (2); dysphagia (2); ascites (2); Herpes Zoster (2); infection (2); pleural effusion (2), and intestinal obstruction (2).

Reviewer comment: Leukopenia and thrombocytopenia (8% each) are likely treatment related. With the information provided, it is not possible to exclude absolutely AEs such as dyspnea, respiratory disorder, urinary tract disorder, or infection having some relation to treatment.

The following AEs were recorded as severe in intensity for one patient each: abdomen enlarged, chest pain; malaise, neck pain, sepsis, arrhythmia, atrial fibrillation, AV block, congestive heart failure, hemorrhage, syncope, biliary atresia, cholelithiasis, dyspepsia, esophageal stenosis, flatulence, gastrointestinal carcinoma, stomatitis, granulocytosis, albuminuria, bilirubinemia, edema, weight loss, bone pain, aphasia, ataxia, confusion, convulsion, hostility, subdural hematoma, apnea, aspiration pneumonia, asthma, cough increased, hypoxia, pharyngitis, pneumonia, sinusitis, skin discoloration, hematuria, kidney calculus, scrotal edema, urinary incontinence, penile disorder, and urinary tract infection

Reviewer comment: Among the AEs recorded as severe intensity for 1 patient each were hemorrhage, asthma, cough increased, hypoxia, pneumonia. Although some of these AEs could be treatment related, it is not possible to say with the information available.

Adverse Events by Treatment Course

The overall pattern of AEs was similar when compared by treatment course. AEs which occurred in more than 15% of the patients who participated in course 1 included asthenia 32 (27.6%), nausea 30 (25.9%), leukopenia 26 (22.4%), pain 24 (20.7%), anemia 24 (20.7%), thrombocytopenia 18 (15.5%), vomiting 18 (15.5%).

Deaths, Other SAEs and Other Significant AEs

The following reviewer table lists SAEs (1 or more) experienced by 59 patients according to type. The distribution of SAEs by treatment site, as determined by the reviewer, is also displayed in Table 12 (see page 29).

Table 14: Number of SAEs by Category

Type of SAE	# of Patients	# of Events
Death*	23	-
Life-threatening	1	-
Requiring or prolonging hospitalization	36	48
Requiring medical intervention	1	-

*Deaths on-study or within 30-120 days of study medicine

Reviewer comment: There are discrepancies in the number of deaths and SAEs throughout the applicant's analysis. These discrepancies are largely due to the failure of the applicant to distinguish between events that occurred within 30 days of treatment or within the 120 day period in the study report. During the last day of the review period, the applicant finally clarified that 5 patients died before being taken off study; 9 patients died within 32 days of last therapy (8 within 30 days, 1 at day 32); 15 patients died within 42 days of last therapy and 23 patients died within 120 days of therapy. The CRF's from all patients dying within 32 days of treatment were reviewed and no definite unreported treatment-related events were detected.

Narrative summaries of all patients with each category of SAE were provided in the study report. Upon FDA request, the applicant also supplied case report forms (CRFs) for patients "who died on study" and patients "who discontinued treatment due to adverse events." The applicant reported there were 9 patients and 18 patients in these respective categories.

The applicant states that the following 5 patients died while on-study: #3-04, #5-02, #7-08, #8-21, and #8-27 and 18 additional patients died between 30 and 120 days of the last dose of study medication. The applicant attributed all the fatal SAEs to disease progression or a serious intercurrent illness, not considered to be related to study medication. The single life-threatening SAE was a patient who had a seizure, felt not treatment related.

Reviewer comment: The following discussion reviews the narratives and CRFs of the 5 patients applicant identified as "deaths on-study", which does not include 3 more patients who died within 30 days. (See page 37, FDA Safety Analysis.) Patients 3-04 and 7-08 are listed in the study report as having died on study, but are not listed among the 9 patients whom the applicant said died on study in the list accompanying the CRFs. The discrepancy is apparently because the applicant does not consistently distinguish "on study or within 30 days" from death at a later time. These patients are included in synopses in the study report of "23 patients who died on-study or between 30 and 120 days" of last study drug. Patient 3-04 had lung cancer, received study drug on 2/10/00, developed lethargy on 3/21, died 4/5/00, felt due to disease. The death was almost 2 months after treatment and not likely associated. Patient 7-08 had metastatic breast cancer to liver, treated on 12/8/99, developed progressive disease on 12/24 with pleural effusion requiring hospitalization. She was discharged 1/14/00, died 1/18/00, 6 weeks post therapy, of progressive disease. Two of the other patients, 8-21 and 8-27 died within days of starting chemotherapy, seeming unrelated, of acute pneumonia and CVA, respectively. These cases probably do not represent treatment related deaths (too early for myelosuppression).

Pt 5-02 had esophageal cancer metastatic to liver and prostate cancer, was treated 1/29/99 and died 2/28/99 with renal failure, death said to be due to disease progression and not treatment related (per investigator, CRF). The last documentation of laboratory studies show normal creatinine, rising alkaline phosphatase, ANC 1.7 on 2/22, the week before death. There is a notation of antibiotics from 2/22 to 2/28 for febrile neutropenia. However the WBC for 2/22 compared to 2/21 seems to have been improving and was not very low. Likely this case does represent disease progression but the information from the terminal hospitalization is not available to document with certainty the contributory factors.

SAEs that Required or Prolonged Hospitalization

The applicant provided narrative summaries for all these patients in the study report.

SAEs that Required Medical Intervention

The applicant reports just 1 patient in this category, a patient with embolus.

SAEs Considered Related to Study Medication

The applicant reports just 2 patients with SAEs attributable to study medication, 1 patient with grade 4 thrombocytopenia, and 1 patient with febrile neutropenia and thrombocytopenia. No cases of hemolytic uremic syndrome (HUS) or pulmonary toxicity were identified.

Laboratory Findings

Hematology and chemistry values were analyzed by shift tables. "The number (%) of patients was counted whose baseline and worst post-baseline on-therapy values fell in the various CTC grades." Fewer than 4% of patients had CTC grade 4 for ANC, WBC, Platelet or hemoglobin. The following applicant's table displays these data for hematology toxicity.

Table 15: Incidence of Post-Baseline On-Therapy Hematologic Toxicity

Analyte	Number (%) of Patients				
	CTC Grade*				
	0	1	2	3	4
WBC Count	41(36.3)	23(20.4)	33(29.2)	15(13.3)	1(0.9)
ANC	48(44.0)	23(21.1)	22(20.2)	13(11.9)	3(2.8)
Platelet Count	36(31.9)	39(34.5)	13(11.5)	22(19.5)	3(2.7)
Hemoglobin	5(4.4)	57(50.4)**	38(33.6)	9(8.0)	4(3.5)

*Values with the worst CTC grade observed during treatment were counted.

** 50 (44.3%) had Grade I at baseline Source: TABLE 5.2, Appendix 2.

A similar analysis is displayed in the following applicant's table for post-baseline liver function test toxicity.

Table 16: Incidence of Post-Baseline On-Therapy Toxicity in Liver Function Tests

Analyte	Number (%) of Patients				
	CTC Grade*				
	0	1	2	3	4
Alkaline Phosphatase	61(64.9)	21(22.3)	5(5.3)	5(5.3)	2(2.1)
AST	65(68.4)	22(23.2)	7(7.4)	1 (1.1)	0(0.0)
ALT	66(93.0)	5(7.0)	0(0.0)	0(0.0)	0(0.0)
Total Bilirubin	86(89.6)	3(3.1)	5(5.2)	2(2.1)	0(0.0)

*Values with the worst CTC observed during treatment were counted. Source: TABLE 5.2, Appendix 2.

Reviewer comment: The applicant did not provide summary tabulation and analysis of changes in renal function tests. See reviewer analysis and discussion below.

Applicant's Summary of Safety

The applicant concluded that the study drug was "safe and generally well-tolerated". Toxicities were similar to those previously reported for MMC, with myelotoxicity most common. Serum creatinine levels were elevated in 13% of patients with normal baseline, but only 2% were greater than grade 2. Nausea and vomiting were reported in 22 and 16%, respectively. Only 1 patient experienced moderate skin necrosis, noted 60 days post treatment. No patients were identified with HUS or pulmonary toxicity. The applicant's analysis demonstrated no evidence of unusual or increased toxicity in this formulation with HPCD, employed for successive cycles.

FDA Safety Analysis

The safety analysis was complicated by contradictions and inaccurate tabulations of numbers of deaths in the study report and subsequent submissions. Late in the review period, the applicant provided clarification for the "number of deaths on study" was variously described as 5, 9, or 23. In correspondence dated 11/12/02, the applicant stated the total number of deaths was actually 9 patients within 32 days of the last dose of therapy (8 patients died within 30 days and 1 on day 32), 7 patients from day 31-42, and, an additional 8 patients who died from day 42-120. In total, 23 patients died up to 120 days following treatment.

The FDA safety analysis was conducted using raw and derived data sets provided exclusively on paper by the applicant. Narratives for all patients with SAEs were reviewed, as well as all CRFs for the 9 patients who "died on study" and selected CRFs of the 18 patients who "discontinued treatment due to AEs." (See detailed discussion of specific patients previous section and below.) The purpose of this audit was to see if drug related causes of death or SAE could be identified by the reviewer, which had not been appreciated by the applicant, who noted only 2 treatment related SAEs.

The applicant provided no derived tables nor analysis of renal function data, although baseline and post-treatment creatinines were available for many, but not all, patients in the data listings by treatment site and patient number (Appendix 3, listing 8). The applicant did summarize the data, stating elevated serum creatinine was "reported in 13% of patients with normal baseline levels but only 2% were greater than Grade 2." Fatal toxicity from MMC is known to occur from the consequences of severe myelotoxicity and from the infrequent, but usually lethal, occurrence of HUS. The excipient in the formulation of MZ, HPCD, in animal studies, has shown acute bladder and renal toxicity. (The occurrence of pancreatic adenocarcinomas in rodents associated with ingestion of high doses for 25 months is not pertinent to the current study population.)

In order to look for a signal suggesting an undetected incidence of HUS or urinary toxicity of MZ, the safety audit included a detailed review of the incidence of abnormal post-treatment levels of serum creatinine and bilirubin. Urinalysis results were also reviewed.

Renal/Bladder Toxicity

For those patients who had both baseline and post-treatment urinalyses, all patients with significant proteinuria or hematuria had these findings pre-treatment as well as post-treatment.

The patient data lists were examined for evidence of post-treatment creatinine elevation above 2 mg/dl. For all patients who had post-therapy creatinine information, only 3 patients had creatinine elevations above 2.0 mg/dl. The following table lists data for these patients.

Table 17: Patients with Post-Treatment Serum Creatinine > 2.0 mg/dl

Patient Number	Baseline (Date)	Post-Treatment (Date)	Comment
06-01	1.1 (11/10/98)	10.6 (12/12/98)	Colon, MZ 11/17, renal obstruction by tumor
11-17	0.7 (5/24/99)	2.1 (01/10/00)	Breast, 4 cycles, last 11/08/99
11-19	1.3 (6/11/99)	2.1 (02/04/00)	Colon, 4 cycles, last 12/06/99

Reviewer comment: The major elevation of creatinine in patient 06-01 is due to disease, renal obstruction due to malignancy. The relatively small increment of creatinine over 8 months is not suggestive of hemolytic uremic syndrome, nor suspicious for any drug toxicity in patients 11-17 and 11-19. Patient 11-19 survived until 12/06/00 and patient 11-17 was still alive with disease as of 4/30/01.

Elevated Bilirubin Post-Treatment

Five patients were identified with elevated total bilirubin post-therapy. These were patients 4-06, 7-03, 7-06, 11-30 and 13-08. The following reviewer chart summarizes the data.

Table 18: Patients with Post-Treatment Total Serum Bilirubin > 2.0 mg/dl

Patient Number	Baseline (Date)	Post-Treatment (Date)	Comment*
04-06	0.7 (9/8/99)	5.3 (10/12/99)	Breast, liver met, MZ 9/15/99, dead 10/25/99 of progressive cancer
07-03	2.0 (4/12/99)	3.7 (6/6/99)	Hepatocellular cancer, MZ 4/19, 6/9/99, SAE neutropenia 5/21, dead 7/4/99 liver failure
07-06	0.5 (7/15/99)	3.7 (8/18/99) 7.2 (8/27/99)	Colon, liver met, MZ 7/15/99, SAE pneumonia 8/27 with leukocytosis, enlarging liver, dead 9/2/99
11-30	0.6 (7/5/00)	2.9 (10/4/00)	Colon, MZ 7/12, 8/30/00, dead 12/25/00, rising alkaline phosphatase, normal platelets
13-08	1.8 (9/28/00)	4.2 (11/8/00)	Colon, MZ 9/28/00, dead 12/21/00, rising alkaline phosphatase, normal platelets

*MZ followed by date(s) refers to date(s) of therapy

Reviewer comment: It should be noted that patient 7-03 had baseline elevation of bilirubin and should have been excluded from this study. However, the findings did suggest progressive cancer involving the liver as the cause of death rather than drug.

Patient 7-03 was treated with MZ 15 mg/m² on 4/19 and 6/9, without dose reduction in spite of SAE neutropenia on 5/21, with platelets 9K on 5/10 (day 21) and 27K on 5/21 (day 32). The last platelet count provided is 88K on 6/16 (day 8). The date of death would have been day 26 of cycle 2. This patient had a bilirubin of 3.7 three days before his second cycle of MZ, which exceeded criteria for retreatment. I cannot exclude some contribution of probable pancytopenia to the patient's demise, but it cannot be documented with the information available

There is no evidence that hemolysis, such as associated with HUS, has caused the elevation of bilirubin in any of these patients. On review of the CRFs, there is evidence of progressive cancer involving the liver as the cause of elevating bilirubin, and no evidence for HUS. However, I do have some concerns about patient 7-03, as discussed above.

CRF Audit

See Reviewer comment top of page 35 discussing the discrepancies in the number of deaths in the applicant's analyses, caused by failure to distinguish between events occurring "on-study", or within 30 days of treatment, or within 120 days. See discussion of clinical details above pertaining to the 5 patients reported in the study report as "dying on-study" (Section "Deaths, Other SAEs"). I agree that those deaths do not appear treatment related although we are lacking some details from the terminal hospitalization

of patient 5-02. The CRFs were reviewed for these patients and patients listed in the tables 17 and 19 discussed in detail, above.

The applicant listed 9 patients as "dying on study" (this time including patients dying within 32 days of treatment) in response to FDA request for those CRFs, which I have reviewed. Cases 3-04 (died 2 months after treatment, off study) and 7-08 (died 6 weeks post therapy of progressive disease), detailed above did not appear on this new list. Patients on both lists, #5-02, 8-21, 8-27, were previously discussed (see page 35). The CRFs of the remaining patients (#4-05, 8-13, 9-08, 1-02, 9-06) provided sufficient information that they died of progressive disease, acute myocardial infarction, and carotid artery blowout due to progressive disease. See discussion regarding patient 7-03 above, following Table 18 (page 39).

Conclusion of Safety Audit of Selected Laboratory Data and CRFs

Reviewer audit did not discover any unreported cases of HUS, study drug related urinary toxicity or definite unreported treatment related deaths.

7.5 Miscellaneous Studies

Study ME001 was conducted at M.D. Anderson Cancer Center in 1996-1997 with intent of demonstrating bioequivalence between MZ and Mutamycin. The data for this study was reviewed as part of the initial submission to the NDA for MZ in 1997. (Medical Review attached in Appendix 3.2.) In a cross-over design, 25 patients received both MZ and Mutamycin, 9 patients received a single course of therapy, and 2 patients received 4 courses of therapy. Patients received a total of 27 courses of MZ and 32 courses of MMC at doses of 23-34 mg. The protocol-specified dose was 15 mg/m². There were no patient deaths on study. There were no significant differences in the incidence of adverse events according to treatment received (MZ or MMC). According to the Medical Reviewer in 1998, Dr. Beitz, "Adverse events reported on study ME001 were consistent with those mentioned in product labeling for MMC, notably granulocytopenia and thrombocytopenia, and other events such as fever, anorexia, nausea, vomiting, headache, and complications of extravasation. There were no reports of overt renal or pulmonary toxicity, and only one report of possible hemolytic uremic syndrome in a patient treated with 4 courses..."

7.6 Literature Review for Safety

The applicant did an adequate literature review, identifying several excellent comprehensive reviews of MMC and referencing several articles which discuss the special toxicities of MMC. The Medical Reviewer searched PubMed, using search terms linking Mitomycin and Clinical Trials and Mitomycin and Toxicity.

7.7 Postmarketing Surveillance - If Applicable.

Not applicable.

7.8 Safety Update - If Available.

The clinical study was completed in September 2000. The NDA resubmission in March 2002 included data further out than 120 days, when available, and provided some death information out to 1 year or more. There was no clear data cut-off date specified and no separate 120-day safety update was provided.

7.9 Drug Withdrawal, Abuse, and Overdose Experience

Not applicable.

7.10 Adequacy of Safety Testing

The applicant is seeking approval for MZ under 505(b)(2) regulations with reference to safety and efficacy of Mutamycin. Mutamycin has been licensed in the U.S. since 1974. As such, the applicant was not required to do detailed safety testing. The 116 patient, phase II clinical trial in patients with advanced cancer showed no unusual or unexpected toxicities at a dose of MZ 15 mg/m² q 6 week. Although this dose is 25% less than the recommended single-agent dose in the Mutamycin label of 20 mg/m², the latter dose is excessively toxic for patients with previous chemotherapy due to the severe and cumulative myelotoxicity observed with MMC.

7.11 Labeling Safety Issues and Postmarketing Commitments

The label should contain the same safety language contained in the label of the parenteral antifungal Sporonox regarding pancreatic adenocarcinoma in rats associated with HPCD, the excipient for both drugs.

Animal studies show bladder toxicity of the excipient, HPCD, when administered I.V. (Rodents were treated with 0.15 g/m² single and repeat dose, and dogs were dosed at 0.5 g/m² HPCD.) There is significant off-label use of MMC by instillation into the bladder weekly for treatment of recurrent superficial transitional cell carcinoma. Doses of up to 40 mg MMC are used weekly, which would result in intravesical exposure of 16 gm HPCD each week if MZ were substituted for generic MMC. The extent of systemic absorption and other safety issues have not been adequately studied for such off label use of MZ. Furthermore, unlike the advanced cancer population, these patients with superficial bladder cancer have the potential for long survival and the possible excess risk of induction of pancreatic malignancy from HPCD is not acceptable. It is hoped that inclusion of detailed animal toxicity information in the label will discourage use of MZ for intravesical therapy.

Pregnancy labeling was updated with preclinical data on fetal toxicity for both MMC and HPCD. Reproductive toxicology for MMC was also included.

The label dose of 20 mg/m² proposed by the applicant was not accepted. The dose of 15 mg/m² will be included in the label, reflecting the dose studied in the MZ clinical trials.

Geriatric labeling was added.

There will not be a request for postmarketing commitment studies.