

8 Dosing, Regimen, and Administration Issues

The prescribing instructions for the reference drug, Mutamycin (and mitomycin generics) state that treatments should be "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 or accumulation 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 inadequate 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. The MMC prescribing instructions state that the doses should be "adjusted accordingly" when used in combination with other myelosuppressive agents, and this is appropriate for MZ, as well. Although study ME2 was not designed to show efficacy, the response rate for this group of patients with diverse cancers was not diminished compared with that described in the original review of Mutamycin.

9 Use in Special Populations

9.1 Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity.

For study ME2, the subject of the current submission, 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.

In study ME001, analyzed for the 1997 filing of the 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 racial data for study ME2 only upon request. Subsequently, upon additional request, the applicant provided, very late in the review process, an analysis of efficacy and safety according to gender, age, and race for study ME2. Once received, it was satisfactory.

The response rate for patients under 65 was (8/60) 14% and (5/56) 9% for patients older than 65, with response status unknown in 5% and 4% of these populations, respectively. By gender, the response rate for males was (8/63) 13% and (5/53) 9% for females. By racial group, the response rate for Caucasian patients was (6/62) 10% and (7/49) 14% for African-American patients. 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, the clinical significance of the comparisons is uncertain.

9.2 Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

No pediatric development is planned. The indications for MZ are in gastric and pancreatic cancer, which are rare in the pediatric population.

9.3 Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

No additional data is required in special populations. MMC is cleared primarily by metabolism in the liver and other tissues. Clearance is inversely proportional to C_{max} due to saturation of pathways. Approximately 10% of MMC is excreted unchanged in urine, but the per cent of drug excreted in urine increases with dose. The excretion of a single I.V. dose of HPCD, the excipient of MZ, is reduced 6-fold in patients with severe renal impairment (clearance ≤ 19 ml/min). For this reason, MZ should not be used in patients with creatinine clearance < 30 ml/min. The label of the innovator drug to which MZ is referenced specifies that "MMC should not be given to patients with a serum creatinine greater than 1.7."

MZ should not be used by women who are pregnant or who are nursing infants, based on preclinical data for both the active ingredient MMC and the excipient HPCD of MZ.

10 Conclusions, Recommendations, and Labeling

10.1 Conclusions Regarding Safety and Efficacy

As a 505(b)(2) application, the applicant is only required to show bioequivalence to Mutamycin, which has been done. The current clinical trial showed similar PK and no excessive or unusual toxicity with sequential cycles of MZ. The applicant is permitted to rely on the efficacy and labeling of Mutamycin for the indication "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." There are no clinical trial data in the label of this product, which was initially approved in 1974. (See section 8.4 for further discussion.) The observed response rate of 11.2% (13/116) in this single arm trial is not worse than suggested in the literature for patients with advanced malignancy of diverse primary sites, although the trial was not designed to show efficacy. 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 in this trial, 211, or 95% were for 15 mg/m² and 218 of 223, or 98%, were for a dose of 15 mg/m² or less.

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

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, 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.

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 _____

_____ (See Chemistry, section 2, for discussion why this claim is unlikely on theoretical grounds.) The study, a single arm trial, cannot be used to support this claim.

There is no evidence that MZ is superior to existing marketed formulations of MMC. There _____ adds any clinical advantage to existing formulations of MMC. For the intended patient population, the possible slightly increased risk from the excipient does not significantly impact on the risk/benefit ratio compared with MMC.

10.2 Recommendations on Approvability

We recommend approval of MZ for the indication in the innovator label. As a 505(b)(2) application, the applicant was only required to show bioequivalence to MMC. This was done by reanalysis of the 1997 study, with exclusion of 1 outlier. The current clinical trial showed no difference in the pharmacokinetics and no excessive or unusual toxicity after sequential cycles of MZ.

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). We recommend approval for MZ at the dose of 15 mg/m². Although MZ is bioequivalent to MMC, 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. Although study ME2 was not designed to demonstrate efficacy, the observed response rate in this heterogeneous group of patients with advanced cancer was not inconsistent with what has been previously been reported for MMC. (See further discussion section 6.4 and 8.)

There is no evidence that MZ is superior to existing marketed formulations of MMC. There is no evidence _____ 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.

10.3 Labeling

As a 505(b)(2) application with reference to the efficacy and safety of Mutamycin, much of the innovator label, including "indications" was preserved, but specific information was added with reference to the excipient in Mitozytrex, HPCD. The efficacy data from the Mitozytrex 116 patient single arm trial was excluded because the trial was not designed to show efficacy, and the data might be misleading. The table of adverse events from the clinical trial was also not included because of the small number of patients compared with the data cited in the innovator label. Preclinical information was added regarding toxicity of the excipient HPCD to bladder and kidneys and carcinogenicity to address concerns about possible off-label use, particularly intravesical therapy in patients with superficial bladder carcinoma.

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.

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Appendix 1

Appendix

1 Individual More Detailed Study Reviews, if Performed

Not Applicable

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Appendix 2

2 Detailed Labeling Changes or Revised Drug Label

For this review, the label is not attached. See labeling contained in Approval letter.

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3 Other Relevant Materials**3.1 Statistical Reviewer's Comments****Statistical Considerations**

In this re-submission of the NDA, the sponsor removed one observation from the analysis for being an "outlier." The FDA biopharmaceutics reviewer accepts the removal of this "outlier" from the analysis.

When an outlier is removed from an analysis, analyses are often performed based on the remaining data pretending the outlier had never existed. This may lead to estimates and standard errors that are incorrect.

The reason for removing any outlier from an analysis is to improve the reliability of the estimates/estimators (reduce the corresponding standard error). The resulting estimator will still be unbiased provided that the criterion for removing an observation is "symmetric," i.e., large differences are removed regardless of the direction of the difference. We will assume that the criterion for removing an observation is symmetric. The variance of estimators based on trimmed statistics can be expressed as the sum of two nonnegative quantities. One of these quantities is estimated by the estimated variance from the analysis with the outlier removed (the analysis ignoring that the outlier ever existed). The other quantity is based on the precise criterion used to remove an observation and the tail distribution for the observations. This quantity can be hard to estimate. In any case, the correct estimate for the standard error (variance) for the estimator based on the trimmed sample should be somewhere between the estimate for the standard error (variance) obtained after removing the outlier (the analysis ignoring that the outlier ever existed) and the estimate for the standard error (variance) obtained before removing the outlier. Here, in every case the standard error estimate obtained after removing the outlier (the analysis ignoring that the outlier ever existed) was smaller than the standard error estimate obtained before removing the outlier. The table below gives log-ratio estimates with their corresponding standard errors for AUC_t , AUC_{∞} , and C_{max} for both before and after the outlier was removed.

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Table 19: Summary of log-ratio estimates with corresponding standard errors

Measurement	Before		After	
	Log-ratio	Std. Error	Log-ratio	Std. Error
AUC _t	0.1116	0.08543	0.06339	0.07807
AUC _∞	0.1204	0.08698	0.07366	0.07970
Cmax	0.1019	0.1115	0.02673	0.09417

The table below gives 90% confidence intervals for AUC_t, AUC_∞, and Cmax. Sensitivity analyses make use of estimates after removing the outlier and standard errors from before removing the outlier.

Table 20: Summary of 90% confidence intervals

Measurement	Before	After	Sensitivity
	90% C.I. (%)	90% C.I. (%)	90% C.I. (%)
AUC _t	96.6-129.4	93.2-121.8	92.0-123.3
AUC _∞	97.2-130.9	93.9-123.4	92.7-124.9
Cmax	91.5-134.0	87.4-120.7	84.8-124.3

We see that all of the 90% confidence intervals from the sensitivity analyses lie within the target limits of 80%-125%.

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3.2 Original Medical Officer Team Leader Review of NDA 50-763 (1998)

Medical Team Leader Review of New Drug Application

NDA # 50-763

MitoExtraTM (Mitomycin for Injection)

SuperGen, Inc.

Des Plaines, IL



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Regulatory Timeline

IND [redacted] Submission:	February 14, 1996
NDA #50-763 Submission:	December 12, 1997
FDA Requests for Information:	February 5 & 6, 1998
Applicant Responses:	February 6 & 8, 1998
NDA Filing Date:	February 11, 1998
Applicant Response to Filing Letter:	February 12, 1998
Revised Product Label:	February 13, 1998
Protocol ME2 (draft) submitted under IND [redacted] (N004):	March 3, 1998
FDA Comments on ME2 draft:	March 27, 1998
FDA Request for Information:	June 24, 1998
Applicant Response:	July 7, 1998
Protocol ME2 (final) submitted under IND [redacted] (N006):	September 4, 1998
FDA Comments on ME2 (final):	September 9, 1998
Clinical Pharmacology Presentation:	November 13, 1998
User Fee Goal Date:	December 12, 1998



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Introduction

SuperGen, Inc., Des Plaines, IL, submitted IND [redacted] on February 14, 1996 for **MitoExtra** (mitomycin for Injection). This IND proposed to study the serum pharmacokinetics, relative bioavailability and urinary excretion pattern of **MitoExtra**, in comparison to mitomycin C.

Mitomycin C, an antitumor antibiotic isolated from *Streptomyces caespitosus*, has been used in clinical trials in the US since 1958. Initial enthusiasm for mitomycin C waned because of the severe, cumulative myelotoxicity encountered when the drug was administered on a daily or every other day schedule. Subsequent studies utilizing a single dose, intermittent schedule demonstrated therapeutic antitumor activity with more manageable and predictable myelotoxicity. Mitomycin C has single agent activity against metastatic gastric, breast and non-small cell lung cancer, with objective response rates in the 20-35% range. Currently, it is approved for the treatment of advanced gastric and pancreatic cancer in combination with other chemotherapeutic agents.

MitoExtra is a reformulation of the currently marketed mitomycin C, replacing mannitol with 20% (w/v) hydroxypropyl-beta-cyclodextrin or HPβCD as the inert excipient. Mitomycin C forms a 1:1 complex with HPβCD at this concentration. The binding of mitomycin C with HPβCD is "loose", probably a "surface-adhering phenomenon" over the HPβCD molecule. The weak binding is expected to result in rapid dissociation of the "complex" when **MitoExtra** is reconstituted and injected parenterally.

HPβCD, — is thought to increase the stability of mitomycin C in solution and to allow more convenient and safe handling in the clinic. Janssen Biotech has carried out the following studies of HPβCD:

HPβCD Pre-Clinical Toxicology. HPβCD is not genotoxic in mutagenicity tests. Two-year carcinogenicity studies were carried out in rats and mice given daily oral doses of HPβCD (500, 2000, or 5000 mg/kg/day).

A major finding is an increase in exocrine pancreatic neoplasms in rats treated at all dose levels, believed to be mediated by cholecystokinin or CCK (HPβCD complexes to bile salts in the gut lumen, resulting in increased release of CCK). CCK, however, is not known to promote cellular proliferation within the pancreas of man, dog or mouse. Second, there was a slight increase in the incidence of neoplasms of the large intestine for rats treated with the highest dose, 5000 mg/kg/day. These tumors were well-differentiated adenocarcinomas that are a part of the rat's adaptive intestinal hypertrophy following high doses of dietary polysaccharides and other nutrients. These changes in rats are known to occur with exposure to nutrients that are generally present in food and are recognized as safe for human consumption. Third, there was an increased occurrence of uterine polyps and mammary gland adenocarcinomas in female rats



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treated at the 2000 and 5000 mg/kg/day doses. Finally, in male mice, there was an increase in the incidence of hepatic neoplasms (data not provided in the Investigational Drug Brochure), although this finding is not considered by Janssen to be a demonstration of a hepatocarcinogenic effect of HP β CD.

Janssen scientists have recommended that "clinical trials of short-term duration should be continued. However, long-term clinical trials (continuous therapy of more than three months or cumulated interval therapy exceeding six months) were not recommended." (Investigational Drug Brochure: **MitoExtra**, prepared 1/24/96, p.18) These restrictions apply only to oral dosing of HP β CD.

HP β CD Clinical Pharmacology. A pharmacokinetic study of HP β CD was performed in three groups of 4 - 8 healthy human volunteers over the dose range of 0.5 to 3.0 g given as a single dose. One group was dosed intravenously with 0.5 - 2.5 g, followed by 1 g orally after one weeks rest. The second group was dosed intravenously with 1.0 - 3 g with one weeks rest between doses, and the third group was dosed orally with 3 g in solution.

HP β CD was well tolerated; headache, nausea and vomiting were noted at the highest dose levels. After intravenous injection, the $t_{1/2}$ was 1.4 ± 0.19 hr, CL_R was 147 ± 25 ml/min, CL_R was 120 ± 32 ml/min, Vd_{0-24} was 16.8 ± 2.6 L, and renal recovery of intact drug was 86-88% in 24 hours. However, after oral dosing, no HP β CD was detectable in plasma signaling that the compound when ingested orally has low bioavailability.

Currently, there are no approved parenteral products that contain HP β CD, however, Janssen's Sporanox (itraconazole) oral solution, a marketed antifungal agent, has been formulated with HP β CD (400 mg/ml). The recommended dose of Sporanox is 20 ml daily for 1 to 2 weeks.

MitoExtra vs. Mitomycin C. The two formulations have equivalent toxicologic profiles in single dose and dose-ranging studies in rats (0.5 - 8 mg/kg). However, in mice, **MitoExtra** at doses of 0.5 - 2.5 mg/kg appeared to be less toxic. **MitoExtra** does not cause significant extravasation in rat and mouse skins, as compared to mitomycin C. **MitoExtra** and mitomycin C have equivalent antitumor activity in C57/BL mice bearing B16 melanoma xenografts. Pharmacokinetic data in rats and mice suggest that the two preparations are bioequivalent.

The phase I study proposed in the IND was a logical next step in the pharmacokinetic evaluation of **MitoExtra** in humans and was allowed to proceed. The significance of the preclinical toxicologic findings (i.e., the multiple types of neoplasms) associated with chronic oral ingestion of the excipient is not known. The proposed study (see details below) specified only a single intravenous dose of **MitoExtra** to be administered to advanced cancer patients, so the risk for the development of new malignancies appeared to be negligible.



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Clinical Protocol ME001

Protocol Title: A Phase I, Bioequivalency Study of **MitoExtra** and Mitomycin C in Cancer Patients with Solid Tumors

Principal Investigator: Richard Pazdur, MD
M.D. Anderson Cancer Center, Houston, TX

The submitted protocol is for a phase I single institution trial in 12 patients with solid tumors refractory to prior therapy. Patients will receive a single dose of either **MitoExtra** or mitomycin C, and then crossover to the alternate agent following a six-week washout period.

Objectives: Establish the single dose serum pharmacokinetics, relative bioavailability and urinary excretion pattern of **MitoExtra** in comparison to mitomycin C in adult patients with refractory malignancies;
Evaluate the safety of **MitoExtra** relative to mitomycin C.

Experimental Design:

Inclusion Criteria: age ≥ 18 years; must have a life expectancy of ≥ 16 weeks and Karnofsky performance status $\geq 60\%$;
must have adequate bone marrow, renal and hepatic function (including, creatinine ≤ 2.0 mg/dl, bilirubin ≤ 1.5 mg/dl and SGPT $\leq 3 \times$ ULN);
must be off all previous chemotherapy or radiotherapy for at least 3 weeks (6 weeks for nitrosourea) and have recovered from any toxic effects of that therapy.

Exclusion Criteria: concurrent anti-cancer therapy;
serious intercurrent illness, severe infection, or gastrointestinal disorders;
pregnancy or lactation.

Baseline Tests: History and physical, performance status, CBC with differential, chemistries, urinalysis, EKG, and determination of disease extent, as appropriate for patient's tumor type.



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Treatment Plan:

MitoExtra or mitomycin C will be administered at a dose of 15 mg/m² IV. SuperGen Inc., Des Plaines, IL, will supply **MitoExtra**. The appropriate dose is reconstituted with Sterile Water for Injection to obtain a 0.5 mg/ml solution. Following a six-week washout period, the alternative drug will be given, again at 15 mg/m² IV. Mitomycin C is commercially available. The first two courses must be given at the **M. D. Anderson Cancer Center**. Patients who have a documented response or stable disease after the first two courses may receive two additional doses of mitomycin C at six-week intervals. All courses will be held pending full hematologic recovery to a granulocyte count ≥ 1500 and platelet count $\geq 100,000$, and complete recovery of non-hematologic toxicities. No dose modifications are permitted in the first two courses; however, dose reductions are permitted in the last two courses for patients continuing on mitomycin C.

Patients will be assessed for a minimum of 24 hours after dosing for injection site reactions, vital signs, urinalysis, serial blood samples for pharmacokinetics, and cumulative urine samples. Patients will be contacted weekly during the washout period for adverse events. The following will be performed at weeks 3 and 5 of each washout period: vital signs, CBC with differential, and urinalysis. Six weeks after course 2, patients will undergo a post-study evaluation analogous to that performed at study entry.

If a patient withdraws from therapy prematurely, they will also undergo post-study evaluation and the reason for early withdrawal will be documented in the case report form.

Pharmacokinetics:

Serial blood samples will be collected at the following time points: pre-dose, 5, 10, 15, 30 and 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, and 5 hours post-dose. Blood samples as well as the 24-hour urine collection will be assayed for mitomycin C concentration using **HPLC**.

Efficacy Considerations:

Although the major point of this study is to evaluate the bioequivalence of **MitoExtra** relative to mitomycin C, patients will be evaluated for tumor response and assigned standard response outcomes (complete response, partial response, no change, and progressive disease).

Statistical Considerations:

No formal statistical analysis is planned.



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ME001 Study Results

The following is a summary of the applicant's study report for ME001 submitted in Section 6.1 under Item 6 (Human Pharmacokinetics) of the NDA. As this is the only clinical study in the NDA, there is no Item 8. No case report forms have been submitted.

Study Conduct. Study ME001 was conducted at the M.D. Anderson Cancer Center from May 29, 1996 to August 11, 1997. Protocol Amendment 2 (dated September 1996) called for an increase in accrual to 27 patients. Protocol Amendment 3 (dated February 1997) called for an increase in accrual to a maximum of 35 patients to ensure enrollment of 27 evaluable patients. In correspondence with the IRB of the M. D. Anderson Cancer Center dated March 10, 1997, the investigator indicated the patient population eligible for this study had already received and progressed on multiple therapies and that some patients had progressed after 6 weeks on study making them inevaluable for pharmacokinetics in the second course.

In accordance with this last amendment, 35 patients were enrolled, but one withdrew before receiving study treatment. A total of twenty-five patients received both **MitoExtra** and mitomycin C in a crossover design, whereas nine patients did not complete the crossover and received a single course of therapy. Two patients received four courses of therapy. A total of 27 courses of **MitoExtra** and 32 courses of mitomycin C were administered. Doses administered of either drug ranged from 23 – 34 mg.

There were no patient deaths on study. Reasons for dropout from the study included: severe thrombocytopenia and hyperbilirubinemia (patient 24), and patient refusal (patient 25), both treated with mitomycin C. Three additional patients withdrew with stable disease. **Reviewer comment:** Reasons for the remaining four dropouts were not provided, but may have been related to disease progression (see above). One of the two patients who received four courses of therapy was diagnosed with possible hemolytic uremic syndrome, a recognized complication of mitomycin C.

Patient Demographics. Of the 34 treated patients, 17 were male and 17 were female. The mean age was 61 years (range 38 – 86 years). Thirty patients were white and four were Hispanic. Baseline performance status (Zubrod Scale) was 0 for six patients, 1 for twenty-five patients, and 2 for three patients. Twenty-nine patients had colorectal carcinoma, two had adenocarcinoma of unknown primary, and there was one case each of carcinoma of the appendix, pancreas and stomach. All but one patient had had prior surgery and all patients had received prior chemotherapy. Eleven patients had received prior radiotherapy. **Reviewer comment:** No details of these prior treatments, such as doses of drugs or radiotherapy administered, were provided.



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Pharmacokinetics. Please refer to the Clinical Pharmacologist's review (Dr. Elena Mishina) of pharmacokinetic parameters and assessment of bioequivalence.

Concomitant Medications. Applicant's Table 7 summarizes the use of concomitant medications for all 34 patients enrolled. The information is not presented by patient. Use of these medications was similar for patients treated with either **MitoExtra** or mitomycin C. A re-tabulation of this data is provided in Applicant's Table 8 by course (1 vs. 2) which again shows no difference in the use of concomitant medications, except for dilaudid use. Significantly more patients used dilaudid during the first course in the study as compared to the second course (6 patients vs. 0; Fisher's Exact $p=0.034$). **Reviewer comment:** Interpretation of this table and others like it in the NDA (e.g., Applicant's Table 10 of adverse events) is problematic since all 34 patients are represented at course 1 whereas only 25 patients are reported for course 2.

Safety. Summary tables of adverse events, blood chemistries and hematologic parameters are presented. The information is not reported by patient. In general, the safety profile of **MitoExtra** is consistent with that of mitomycin C. Applicant's Tables 9 and 10 summarize adverse events for all 34 patients who received a total of 32 courses of mitomycin C and 27 courses of **MitoExtra**. Events are listed by preferred term as reported by the investigator.

The table below summarizes adverse events that were reported in at least two patients treated with **MitoExtra**. Only those events that occurred with higher frequency on **MitoExtra** than on mitomycin C are reported. Percentages of patients are rounded off. There were no significant differences noted between treatment groups in these events.

Adverse Event	Mitomycin C N= 32 (% of patients)	MitoExtra N= 27 (% of patients)
Abdominal Cramps	3	7
Anemia	6	15
Chest Pain	4	7
Conjunctivitis	0	7
Dysgeusia	0	7
Dyspnea	6	15
Fatigue	53	56
Motor	6	7
Pain, rectal	0	7
Skin Reaction	3	7



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Vomiting	22	26
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The table below summarizes adverse events that were reported in at least two patients treated with mitomycin C. Only those events that occurred with higher frequency on mitomycin C than on **MitoExtra** are reported. Percentages of patients are rounded off. There were no significant differences noted between treatment groups in these events, except for headache, which was reported in 6/32 patients treated with mitomycin C vs. 0/27 patients treated with **MitoExtra**. There was one severe extravasation reported on mitomycin C, no extravasations on **MitoExtra**.

Adverse Event	Mitomycin C N= 32 (% of patients)	MitoExtra N= 27 (% of patients)
Abdominal Pain	25	19
Anorexia	16	11
Ascites	9	0
Constipation	9	7
Cough	13	7
Diarrhea	16	11
Dizziness	6	4
Peripheral edema	9	4
Fever, unknown	28	22
Flu-like syndrome	6	4
Headache	19	0*
Infection	9	7
Insomnia	9	0
Local reaction	6	4
Nausea	47	33
Pain	16	7
Pain, extremity	6	4
Pain, joint	6	0

*Fisher's Exact $p=0.027$



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Reviewer comments: No information has been provided on the severity grading of adverse events, drug-relatedness of events, supportive measures taken, duration of events, whether the event resolved or was ongoing at last follow-up, etc.

Applicant's Tables 11 and 12 summarize adverse events for the subset of 25 patients who completed both legs of the crossover. There were no significant differences in the incidence of adverse events in these patients by treatment received.

The incidence and severity of laboratory abnormalities were reported by severity grade using Common Toxicity Criteria and are summarized in the table below (adapted from Applicant's Tables 15 and 16). There were no significant differences in the incidence or severity of these abnormalities in the two treatment groups. **Reviewer comment:** The number of patients evaluable for hematologic parameters is 32, whereas 28 patients were evaluable for liver function tests, and 33 for renal parameters.

Laboratory Parameter	Mitomycin C (% of patients)		MitoExtra (% of patients)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
WBC	59	9	63	4
ANC	34	6 ^a	48	8 ^a
Hemoglobin	100	3	100	4
Platelets	75	16 ^a	74	19 ^a
Bilirubin	15	8	13	9 ^b
Alk Phos	58	12	48	4
SGOT	50	4	43	4
SGPT	23	0	17	0

^a one patient with grade 4 toxicity

^b two patients with grade 4 toxicity

At FDA's request, the applicant provided information on BUN and creatinine levels observed on study. On mitomycin C, BUN levels were normal in 71% of patients, low in 19% and high in 10%. On MitoExtra, these levels were 81%, 15%, and 4%, respectively. On both mitomycin C and MitoExtra arms, serum creatinine levels were normal in 48% of patients and low in 52%.

At FDA's request, the applicant provided additional clinical information regarding the two patients who developed grade 4 hyperbilirubinemia on MitoExtra:

Patient 1 was a 50 year-old male patient with colorectal cancer metastatic to liver and serosal lymph nodes and a Zubrod score of 2 at study entry. At baseline, this patient had abnormal elevations of alkaline phosphatase (342), LDH (6653), SGOT (144) and SGPT (61), although total bilirubin was normal (1.1). On day 15 following administration of 34 mg of MitoExtra, all liver function tests were improved. The alkaline phosphatase declined to 241, the LDH to 875,



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the SGOT to 79 and the SGPT to 28. Total bilirubin was 0.8. However, on day 41, all parameters worsened, including a rise in the total bilirubin to 3.5. Coincident with these changes was a > 50% rise in CEA and progression of known liver metastases as well as appearance of new lesions on CT scan. The applicant concluded that the hyperbilirubinemia was due to disease progression and was not drug related. FDA agrees with this assessment.

Patient 18 was a 49 year-old male with rectal cancer metastatic to liver and lymph nodes and a Zubrod score of 1 at baseline. On day 1, this patient had abnormal elevations of alkaline phosphatase (678), LDH (1762), SGOT (111) and SGPT (139), although total bilirubin was normal (0.9). On day 38 following administration of 29 mg of MitoExtra, the total bilirubin had risen to 9.5 and the alkaline phosphatase to 744. The SGOT was unchanged. CT scan confirmed progression of hepatic metastases and biliary duct dilatation, likely due to metastases at the porta hepatis. The applicant concluded that the hyperbilirubinemia was due to disease progression and was not drug related. FDA agrees with this assessment.

Reviewer comments: Adverse events reported on study ME001 were consistent with those mentioned in product labeling for mitomycin C, notably granulocytopenia and thrombocytopenia, and other events such 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 four courses (estimated total dose = 60 mg/m²).

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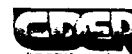
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Applicant's Conclusions:

- Tests of bioequivalence in the major pharmacokinetic parameters confirm the preclinical findings that **MitoExtra** and mitomycin C are bioequivalent.
- There were no unexpected adverse events observed. Furthermore, the toxicity profile may be viewed as a surrogate for biologic activity.

Conclusions of FDA Review Team:

- Using two one-sided t-test procedures for analysis of AUC_t , AUC_{inf} , and C_{max} , the FDA Clinical Pharmacology review staff were unable to reproduce the applicant's tests for bioequivalence. In fact, in Study ME001, mean values for AUC_{inf} and C_{max} for **MitoExtra** were about 18% higher than for mitomycin C. The variability in pharmacokinetic profiles of **MitoExtra** and mitomycin C may be explained by the substitution of mannitol with Hp β CD, or by as yet unidentified factors that have resulted in poor study conduct.
- Convincing data demonstrating that **MitoExtra** undergoes rapid *in vivo* dissociation has not been submitted in the NDA. If there is no methodology available to definitively resolve this issue, enabling the demonstration that mitomycin C rapidly dissociates from Hp β CD and circulates as free drug, then safety and efficacy data from clinical trials to prove the equivalence of **MitoExtra** to mitomycin C will become necessary. (Conveyed to applicant on March 27, 1997; second request for information made June 24, 1998)
- In Study ME001, the safety profiles of **MitoExtra** and mitomycin C in patients with refractory solid tumors do appear to be similar, however, this impression is based primarily on reports of acute toxicity in 27 patients treated with a single dose of **MitoExtra**. The safety profile of **MitoExtra** on repeat dosing has not been evaluated. In clinical practice, it is anticipated that **MitoExtra**, if approved, will be administered for several cycles, albeit, at somewhat lower doses, in combination with other cytotoxic agents.
- At the time of NDA filing (February 11, 1998), FDA informed the applicant that prior to full marketing approval, we would require a clinical study in solid tumor patients receiving multiple doses of **MitoExtra** in order to confirm that **MitoExtra** does not pose any unique safety risks. The applicant was invited to submit a draft protocol so that agreement on the design and goals of this study could be reached. Results of pharmacokinetic and safety evaluations in sufficient numbers of patients would have to be submitted for FDA review. The applicant's proposal of 7/7/98 to conduct this study as a post-approval commitment and limit initial product labeling for **MitoExtra** to two cycles of therapy pending satisfactory completion of this study is not acceptable.



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Clinical Protocol ME2

Protocol Title: A Study of the Tolerance and Efficacy of **MitoExtra** in Patients with Solid Tumors who Have Failed Previous Therapy

Principal Investigator: John S. MacDonald, MD
Saint Vincent's Comprehensive Cancer Center, New York, NY

The final version of this protocol, submitted on 9/4/98, incorporates the FDA's comments on an earlier draft version that were conveyed on March 27, 1998. The protocol is for a single arm, phase I/II single institution trial in 20 (14 fully evaluable) patients with solid tumors refractory to prior chemotherapy. Patients will receive a minimum of three courses of **MitoExtra**. Additional courses may be given assuming disease progression or unacceptable toxicity have not been observed, or a cumulative dose of 60 mg/m² of mitomycin C has not been exceeded.

Objectives:

- To test the possibility of a 20% or higher frequency of unexpected or unexpectedly severe toxicities with **MitoExtra** treatment.
- To acquire experience in the use of **MitoExtra** and a description of toxicity and response.
- To investigate the PK of mitomycin following **MitoExtra** administration, comparing successive courses of treatment.

Experimental Design:

Inclusion Criteria:

- age $\geq$ 18 years; must have a life expectancy of $\geq$ 16 weeks and ECOG/ Zubrod performance status of 2 or less;
- must have adequate bone marrow, renal and hepatic function (including, creatinine $\leq$ 1.7 mg/dl, bilirubin $\leq$ 1.5 mg/dl and alkaline phosphatase, SGOT and SGPT $\leq$ 2 x ULN);
- if the SGOT/SGPT elevation is tumor-related, then elevations up to 4 times the norm are acceptable, provided the bilirubin $<$ 3.0 mg/dl;
- must be off all previous chemotherapy or radiotherapy for at least 3 weeks (6 weeks for nitrosourea) and have recovered from any toxic effects of that therapy.

Exclusion Criteria:

- concurrent anti-cancer therapy; prior mitomycin therapy;
- serious intercurrent illness, severe infection, gastrointestinal disorders, or other malignancy; patients with brain metastases;
- pregnancy or lactation.



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Baseline Tests:

History and physical, performance status, CBC with differential, chemistries, urinalysis, EKG, and determination of disease extent, as appropriate for patient's tumor type, pregnancy test.

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Treatment Plan:

MitoExtra will be administered at a dose of 15 mg/m² IV over 30 minutes every 6 weeks. MitoExtra will be supplied by SuperGen Inc., Des Plaines, IL. Each vial is reconstituted with 8.5 ml of Sterile Water for Injection to obtain a 0.5 mg/ml solution.

All courses will be held pending recovery of laboratory values (ANC $\geq$ 1000 and platelets $\geq$ 100,000) and other comorbid illness to baseline levels. Treatment may be delayed for up to 3 weeks, with weekly blood counts and other examinations as indicated, while waiting for patient recovery. Patients who do not recover within 3 weeks will be taken off study. A 25% dose reduction is recommended if, in the previous course, 1) the nadir ANC was $<$ 500 or the nadir platelet count $<$ 25,000, or 2) neutropenia was accompanied by fever, or 3) treatment was delayed for $>$ 2 weeks for hematologic recovery.

The following will be performed every other course of therapy: history, physical examination, performance status, vital signs, CBC with differential, urinalysis, CXR, evaluation of tumor status. Adverse events will be graded using NCI Common Toxicity Criteria.

If a patient withdraws from therapy prematurely, they will also undergo post-study evaluation and the reason for early withdrawal will be documented in the case report form.

Pharmacokinetics:

Serial blood samples will be collected from 12 patients at the first and second (or third) courses at the following time points: pre-dose, 5, 10, 15, and 30 minutes, and 1, 2, 4, and 6 hours post-dose. Blood samples as well as 24-hour urine collections will be assayed for mitomycin C concentration using HPLC.

Efficacy Considerations:

Although the major endpoints of this study are to evaluate the tolerability and pharmacokinetics of multiple courses of MitoExtra, patients will be evaluated for tumor response and assigned standard response outcomes (complete response, partial response, no change, and progressive disease).

Statistical Considerations:

Using Gehan's formula, if 14 evaluable patients (20 total) are recruited to this study, the probability that none of them will present with an unexpected event is less than 5%.

ME2 Study Results

On June 24, 1998, FDA requested that the applicant provide the approximate start date of the ME2 study, the estimated rate of accrual to the study, and timeframe for submission of the study report to the FDA for review.



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The applicant responded (7/7/98) that the ME2 study would begin in August 1998 and that the accrual rate is expected to be about 6 patients per month. Complete accrual and treatment of all patients is expected by March 1999 and the study report would be submitted to the FDA in May 1999.

As the user fee date for this NDA submission is December 12, 1998, the applicant requested that the FDA grant marketing approval of MitoExtra based on the results of the ME001 study. The applicant proposed that it would revise the package insert to include a statement that MitoExtra should not be administered for more than two cycles. The applicant also proposed to conduct the ME2 study as a "post-approval commitment" and to revise the package insert to address dosing for more than two cycles upon completion and FDA review of the ME2 study.

Review of Product Label

The product label submitted in the NDA contains the identical wording as for Bristol Myers Squibb's marketed mitomycin C for injection, except for details specific to MitoExtra in the Description, and Dosage and Administration sections. At the time of NDA filing, FDA requested (2/11/98) that the label be revised to incorporate "appropriate references which address current data regarding reprotoxicity, carcinogenicity, and mutagenicity of MitoExtra". On February 13, 1998, a revised label was submitted that was identical to the original label.

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Recommended Regulatory Action

The information submitted in NDA # 50-763 by SuperGen, Inc., for MitoExtra™ (Mitomycin for Injection) is inadequate and the application should not be approvable under section 505 (d) of the Act and 21 CFR 314.125 (b) (9). The deficiencies may be summarized as follows:

- There is insufficient evidence in the data presented to conclude that MitoExtra is bioequivalent to mitomycin C, as required under 21 CFR 320.23 (a) (1). Using two one-sided t-test procedures for analysis of AUC_t , AUC_{inf} , and C_{max} , bioequivalence of MitoExtra and mitomycin C could not be demonstrated based on comparisons of the 90% confidence intervals for AUC_t (96.6 – 129.4%), AUC_{inf} (97.3 – 130.9%), and C_{max} (91.5 – 134.0%).
- FDA does not consider the test of bioequivalence based on the 20/20 rule for the confidence interval an acceptable statistical technique. Utilization of this technique does not fulfil the criteria specified in 21 CFR 320.23 (a) (2).
- There was considerable variability in the pharmacokinetic parameters studied. Coefficients of variation (CV) for MitoExtra were 65% for AUC_t , 64% for AUC_{inf} , and 86% for C_{max} ; whereas, for mitomycin C, CV were 31%, 32% and 44% for these parameters, respectively. The mean values for AUC_{inf} and C_{max} for MitoExtra were about 18% higher than for mitomycin C. These findings may be explained by the substitution of mannitol with HpbCD, or by as yet unidentified factors that have resulted in poor study conduct.

We have the following additional requests for information that should be addressed if the application is resubmitted:

- A re-analysis of study ME001 should be performed using statistical procedures described in the Agency's guidance document entitled, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design". Additional references include Schuirmann, D. J., J Pharmacokin Biopharm 1987: 715:657-680; and Rosner, B., Hypothesis Testing: Two-Sample Inference in Fundamentals of Biostatistics, PWS-Kent Publishing Co., Boston, MA, third edition. Patients considered outliers on statistical grounds should be further explored from a physiologic standpoint to provide justification for their exclusion from the re-analysis of this study. Alternatively, a new study demonstrating bioequivalence of MitoExtra™ and mitomycin C should be performed.
- The pharmacokinetics of MitoExtra™ should be studied in consecutive cycles of therapy as the applicant has proposed in study ME2. Considering that MitoExtra™, if approved would be administered for multiple cycles, and that circulating HpbCD derivatives may influence the distribution and elimination of other co-administered drugs, the applicant is encouraged to obtain blood samples for the pharmacokinetic evaluation of MitoExtra™ in the second and/or third cycles of treatment. Alternatively, a repeat cycle toxicology study in animals to confirm that MitoExtra™ does not pose a worse safety profile relative to mitomycin C could be performed. This study should incorporate toxicokinetics.



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- A revised package insert should be submitted that describes the results of bioequivalence and other clinical studies performed with MitoExtra™. The package insert should also incorporate available data regarding the reprotoxicity, carcinogenicity, and mutagenicity of mitomycin C.
- The Agency's Labeling and Nomenclature Committee will review the proposed name, MitoExtra™, for appropriateness. The use of the suffix "Extra" might convey clinical benefits that are not or cannot be substantiated by data, or may be considered inappropriate.

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

/S/

Julie Beitz, MD Date

/S/

Robert Justice, MD Date

cc:

IND #

HFD-150/ Division File

HFD-150/ J. Beitz

HFD-150/ D. Griebel

HFD-150/ D. Catterson

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3.3 Study Sites

List of Participating Investigators

Site No.	Investigator (No. of Patients Treated)
1	Luis Meza, MD. (5 patients) Southwest oncology Research 155 hospital Drive, Ste.101 Lafayette, LA 70503 (318)234-4535
2	Hal Gerstein, MD. (3 patients) Medical Oncology and Hematology 170 Great Neck Road Ste.100 Great Neck NY 11022 (516) 773-3708
3	Clarence B. Vaughn, MD. (6 patients) Southfield Oncology Institute 21751 West Eleven Mile Road Southfield, MI 49076 (249) 356-2829
4	Arnold Wax, M.D. (6 patients) 3920 South Eastern Ave., Suite 200 Las Vegas, NV 89119 (702) 369-4604
5	John B. Craig, MD. (8 patients) Schumpert Cancer Treatment Center One St Mary Place Shreveport LA 71101 (318)6914139
6	Cary Gota, MD. (1 patient) LA Hematology/Oncology Group 1245 Wilshire #303 Los Angeles, CA 90017 (213) 977-1214
7	Francisco Gonzales, M.D. (8 patients) USC School of Medicine Center for Cancer Treatment and Research Palmetto Richland Memorial Hospital Seven Medical Park, Suite 202 Columbia SC 29203 (803) 434-3673

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8	
9	John J. Petrus, M.D. (9 patients) The Cancer Center 224 West Exchange Street Ste. 150 Akron, OH 44302 (330) 384-6431
11	Kai-Yiu Yeung, MD (28 patients)* Oncology-Hematology Associates 8926 Woodyard Road, Suite 201 Clinton, MD 20735 (301) 868-7911
12	Jerome Rubin, MD. (2 patients) 700 Cass Street, Suite 122 Monterey, CA 93940 (831) 375-4777
13	John MacDonald, MD. (9 patients)** Saint Vincent's Hospital 153 West 11th Street New York, NY 10011 (212) 604-2219
14	Grant Swanson, M.D. (1 patient) Monterey Bay Oncology 261 El Dorado #202 Monterey, CA 93940-2911 (831) 375-4105

*Site No. 11 also enrolled 6 patients who were never treated.

**Site No. 13 also enrolled 1 patient who was never treated.

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