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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-763

Pharmacology Review(s)

To: Grant Williams
Deputy Director, DODP

From: John Leighton
Supervisory Pharmacologist

Subject: NDA 50-763
Mitomycin C with cyclodextran

Date: November 8, 2002

Introduction

MitoExtra is a reformulation of mitomycin C with hydroxypropyl-β-cyclodextran (HPβCD) substituted for mannitol as an excipient. Preclinical toxicology studies were conducted to support this change; the studies conducted in rats and dogs indicate that the two formulations are about equivalent in toxicity. The toxicology of mitomycin C and HPβCD alone were also reviewed by Dr. Brower, and the findings are summarized in her NDA review.

Review of Draft Pharmacology/Toxicology Safety Issues

Dr. Brower has addressed all the pharmacology and toxicology issues with this submission and no issues remain to be addressed. Dr. Brower has concluded, and I concur, that the application is approvable from a pharmacology/toxicology perspective.

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/s/

John Leighton
11/8/02 05:21:20 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 50-763
Review number: 2 (Label review included as appendix – Section X..)
Sequence number/Date/Type of submission: 000/March-October 2002 NDA
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: SuperGen, Inc.
Dublin, CA 94568

Manufacturer for drug substance : [redacted]

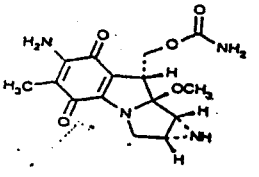
Manufacturer for drug substance changed in submission of 10/10/02: [redacted]

Manufacturer for drug product: [redacted]

Reviewer Name: Margaret E. Brower, Ph. D.
Division Name: Division of Oncology Drug Products
HFD #: 150
Review completion date: November 6, 2002

Drug:

Trade name: MitoExtra
Generic name (list alphabetically): Mitomycin C, Mutamycin with hydroxypropyl-β-cyclodextrin (HPβCD) as replacement inert excipient
Chemical name: 7-amino-9-methoxymitosane
CAS registry number: 50-07-7
Mole file number: n/a
Molecular formula/molecular weight: $C_{15}H_{18}N_4O_5$/ MW =334.33
Structure:



Relevant INDs/NDAs/DMFs: IND [redacted] DMFs [redacted]

Prior Reviews: IND [redacted] M. Brower, 2/96; NDA 50-450: S. Bader, 6/72

Drug class: Cytotoxic

Indication: "MitoExtra 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 combination with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed."

Clinical formulation: Vial containing 5 mg mitomycin with 2 g HPCD

Route of administration: intravenous

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The NDA for MitoExtra is approvable from a Pharmacology/Toxicology perspective with label changes as described under Recommendations on Labeling.

B. Recommendation for Nonclinical Studies

Studies for mitomycin C as well as HPβCD were summarized from literature references as well as previous collected data. See study summaries as well as drug label.

C. Recommendations on Labeling

See attached label corrections.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Changes were observed in the kidney, urinary bladder and lungs of rodent and nonrodent species following administration of HPβCD and single-dose preclinical studies with MME resulted in many similar findings. It thus appears that toxicities due to HPβCD may occur following administration of MME. In addition, carcinogenicity of the pancreas was a result of extended dosing with iv HPβCD in rodents. HPβCD administered orally at $12g/m^2$ caused pancreatic lesions in rats. MMC is mutagenic, clastogenic, carcinogenic and teratogenic.

B. Pharmacologic Activity

MitoExtra is a reformulation of mitomycin C with hydroxypropyl-B-cyclodextrin (HPβCD) substituted for mannitol in the iv solution. According to the sponsor, the purpose of the change in excipient to HPβCD is improved stability and solubility of MitoExtra. (Both of these rationale have been called into question by CMC during the review of this NDA). Mitomycin C is a bifunctional DNA alkylator, and as such, inhibits the replication/transcription of DNA.

C.Nonclinical Safety Issues Relevant to Clinical Use

Mitomycin C is mutagenic, clastogenic, carcinogenic and teratogenic. The substituted excipient, HPβCD, is also carcinogenic and teratogenic and has been associated with bladder toxicity and nephrotoxicity in rodents and non-rodents.

III. Administrative

A. Reviewer signature: /S/

B. Supervisor signature: Concurrence - /S/

Non-Concurrence - /S/

C. cc: list
LeightonJ
BrowerM
ScherN
AtkinsB

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. **PHARMACOLOGY:** No additional data submitted.
II. **SAFETY PHARMACOLOGY:** No additional data submitted.
III. **PHARMACOKINETICS/TOXICOKINETICS:** No additional data submitted.
IV. **GENERAL TOXICOLOGY**

Summary of single dose studies, comparative extravasation and skin ulceration (Key results from study reviews under IND [redacted])
Single dose studies comparing mitomycin and MitoExtra in mice at doses of 1.5, 7.5 and 24mg/m^2 resulted in increased incidence of renal tubular karyomegaly and stomach hyperplasia in MD and HD MitoExtra-dosed animals. However, mortality was increased for HD mitomycin-dosed mice (12/12) compared to HD MitoExtra (7/12). Single-dose studies comparing the two drugs in rats at doses of 3, 6 and 15mg/m^2 resulted in increased incidence of lung congestion and gastric granuloma in HD MitoExtra-dosed Γ and E. Liver enzymes (ALT, AST and GGT) were significantly elevated in MitoExtra-dosed E rats. Even though the extravasation toxicity study performed in rats indicated decreased lesion diameter of the skin with MitoExtra, injection site ulceration and acanthosis in mice and E rats was equal to or greater than that observed with mitomycin C in comparative single dose studies. In rodents, it appears that MitoExtra is bioequivalent to mitomycin C. (Specific study titles listed below).

Single Dose Toxicity

- **Effects of hydroxypropylcyclodextrin on Mitomycin-C solubility and extravasation toxicity in rats.** Conducted by [redacted]
Findings: Intradermal administration of Mitomycin C and MitoExtra: extravasation for MME ~60% less than MMC over 6d (Dose 2.5mg/mL) *no histopathology; no line listings*

Comment: It appears that a second extravasation study was included in the Investigational Drug Brochure included with the NDA. There was no comment on the extravasation study submitted and reviewed with the IND. The sponsor has been asked to comment, but no response has been received. Update: Comment received on 11/8/2002, indicating that studies were a preliminary and final version of the same study. However, differences in doses and days on which lesions were measured does not correlate with original IND study review.

Summary findings of additional comment on extravasation issue: 1 or 5mg MMC and MME administered intradermally evaluated for comparison on days 1, 4, 7, and 14 (also indicated to be measured on days 3 and 17 in fax received on 11/8/02 – no correlation of timing). Rats treated with MMC +20% HPβCD exhibited reduced lesion size in LD group + reduced incidence of animals with lesions (i.e. 1/12 with HPβCD compared to 12/12 without); no difference in HD group. 30-40% HPβCD further reduced lesions as compared to MMC alone (no specifics were submitted). MME at 1mg comparative to lesions of MMC at 5mg.

- **Effects of Hydroxypropyl-beta-cyclodextrin on Mitomycin C dermal toxicity in rats.** Conducted by [redacted] **Supergen.**
Findings: Mitomycin C must be pre-complexed with cyclodextrin to reduce the incidence and severity of skin lesions.

2-Y29 A Pilot Study of Mitomycin C following intravenous administration to CD-1 mice. Conducted by .

2-Y30 A Pilot Study of Mitomycin C following intravenous administration to Sprague-Dawley rats. Conducted by

2-Y31 A Single Dose Toxicity Study of Mitomycin C and MitoExtra following intravenous administration to CD-1 mice. Conducted by
Findings: Incidence of skin ulceration (2/6 compared to 1/6), acanthosis (2/6 compared to 1/6), chronic inflammation (0/6 compared to 1/6) >MME compared to MMC at 2.5mg/kg (drug administration to tail vein). See summary above.

2-Y32 A Single Dose Toxicity Study of Mitomycin C and MitoExtra following intravenous administration to Sprague-Dawley rats. Conducted by

Findings: Incidence of skin ulceration >MME at 2.5mg/kg (2/5) compared to MMC (0/5) (drug administration to tail vein). See summary above.

Multiple Dose Toxicity

7041-100 43-day Intravenous toxicity and toxicokinetic study with Mutamycin and Mitomycin Extra in dogs. Conducted by according to GLP. In life study completed 1999; interim study report submitted 9/5/2002 (Final report received by CDR 10/11/2002)

Study History: Study proposed by agency in 1998 in order to demonstrate claim of extravasation , compare toxicokinetics (bioequivalence) of MME and MMC, and provide evidence confirming that repeat doses of MME do not pose a worse safety profile compared to MMC. On d1, dogs administered MME received only 84-87% of the target dose.

Findings: Toxicokinetics were similar between MMC and MME. Other than findings of inflammation, fibrosis, and "purulent sores" at the catheter site of MME animals (see below for comparative table), MMC and MME appeared to be similar. A more detailed review of the dog study would not impact the conclusions of this NDA.

Species: beagle dog
#/sex/group: 6 males/group
Age: 6-7months
Weight: 7.4-11.2kg
Drug: Mitomycin (MMC); MitoExtra (MME)
Dose: 0.2, 0.5mg/kg/day dosed days 1, 22 and 42
Note: Day 1 MME 0.2mg/kg dogs received 84-87% of intended dose volume; 0.5mg/kg dogs received 88-89% of intended dose volume; Day 42 MMC 1/6 0.2mg/kg dogs received 87% of target volume
Route and volume: iv; dose volume: 2 and 5mL/kg according to dose

Mortality and clinical observations: 2/6 dogs died or were sacrificed moribund in HD MMC and HD MME groups. MME dogs (0.5mg/kg) sacrificed moribund d34: "several purulent sores"; "chronic inflammation and fibrosis associated with catheter sites"

Catheter site findings:

The issue of extravasation was not specifically addressed. Chronic inflammation and fibrosis was observed at the infusion sites (catheter entrance site into thorax and exit site near implanted infusion port); mean severity of findings was greater with MME for fibrosis of catheter entrance, and inflammation and fibrosis of catheter exit. In other cases, findings were similar between MMC and MME. The sponsor indicated that lesions were related to physical trauma associated with surgical catheter placement and that the biological significance of these findings to treatment is not clear compared to uncathetered control sites of dosed animals. However, findings at the catheter sites, as indicated below, appear to be a result of the site administration or "leakage" of the comparative drugs, although inflammation and fibrosis at the catheter sites may have enhanced these effects. Examination of control sites was not reported.

Incidence and severity of histopathological findings of catheter sites (N=6/group)

Catheter site/finding	LD MMC	HD MMC	LD MME	HD MME
Catheter entrance/chronic inflammation				
Unremarkable-minimal	1	5	2	2
Slight	5	1	4	4
Mean Severity grade	1.8	1.0	1.5	1.3
/fibrosis				
Unremarkable-slight	4	6	4	4
Moderate	2	0	2	2
Mean Severity grade	2.3	1.7	2.3	2.0
Catheter Exit/chronic inflammation[a]				
Unremarkable/minimal	5	5	4	4
Slight	1	1	2	1
Moderate	0	0	0	1
Mean severity grade	0.8	0.8	1.0	1.2
/fibrosis				
Unremarkable-minimal	3	2	2	1
Slight	3	4	3	3
Moderate	0	0	1	2
Mean severity grade	1.3	1.3	1.5	2.0
Catheter tip/venuous intimal proliferation[b]				
Unremarkable-minimal	1	3	1	1
Slight	0	1	3	4
Moderate	4	2	1	1
Moderately severe	1	0	0	0
Mean severity grade	2.8	1.7	1.7	1.8
/thrombus		3		1

LD MMC= 0.2mg/kg MMC
HD MMC= 0.5mg/kg MMC
LD MME= 0.2mg/kg MME
HD MME= 0.5mg/kgMME
[a]HD MMC group, N=4; LD MME group, N=3
[b]LD MMC group, N=5

Hydroxypropyl-beta-cyclodextrin (HPβCD) (excipient for MME)

Hydroxypropyl-beta-cyclodextrin has replaced mannitol as the inert excipient in MitoExtra at a concentation of 2g HPβCD/5mg MMC. Preclinical oral and intravenous toxicity studies conducted with HPβCD were reviewed by O.McMaster, Ph.D., HFD-530 in 1996 and are summarized below. Additional data were reviewed and exerpted from DMF [redacted]

Confidential information obtained from DMFs.

Target Sites: Data summarized from literature references as indicated.

When administered intraveneously, HPβCD is primarily excreted via the kidneys in rodents and dogs; greater than 90% is excreted within 4h of dosing (Stratton, CE. 1992. 2-hydroxypropyl-β-cyclodextrin, safety and manufacturing issues. Pharmaceu. Technol.p.1830). The nephrotoxicity (glomerular and renal tubular necrosis) observed following parenteral administration of HPβCD in rats and rabbits appears to be the result of accumulation and recrystallization of the drug in the proximal tubules of the kidney (Albers and Muller. 1995. Cyclodextrin derivatives in pharmaceutics. Crit.Rev.Therapeu. Drug Carrier Systems. 12: 311; Stratton. 1992.). Cyclodextrins, primarily HPβCD, are also found to cause hemolysis of human erythrocytes as a consequence of membrane disruption; membrane disruption is caused by the release and removal of membrane components (cholesterol and proteins) (Albers and Muller. 1995.)

In separate studies, single and repeated dose administration of HPβCD on the bladder of rodents at doses as low as 0.15g/m2 included findings of swollen epithelial cells, swollen lysosomes with inclusions and stones with associated metaplasia. Findings persisted following 3months of recovery. Kidneys appeared swollen and granular.

Dogs administered doses as low as 0.5g/m^2 HPβCD exhibited findings of urinary bladder edema, lysosomes and inclusions of epithelial cells of the kidney. As with rodents, findings persisted after 3 months recovery.

V. GENETIC TOXICOLOGY

No additional data submitted. See label for review of genetic toxicology of MMC as summarized from literature references. HPβCD was not mutagenic.

VI. CARCINOGENICITY

No additional data submitted. See label for review of carcinogenicity of MMC and HPβCD as summarized from literature and previous documentation.

The carcinogenicity of HPBCD was assessed in rats at doses of 3, 12 and 30g/m^2 administered in the feed for 25 months. An increase in the incidence of adenomas and adenocarcinomas of the exocrine pancreas were observed at 2 weeks, 12 months and 25 months; the incidence was statistically significant ($p<0.05$, $p<0.01$) in all dosed males and MD and HD E. Dose-related decreased cholesterol (2-fold), triglycerides and phospholipids were observed, as well as increases in transaminases. The sponsor speculated that increased incidence of pancreatic adenomas were secondary to maldigestion which caused increased cholecystokinin release and stimulated pancreatic cell division which could occur in rodents but not in humans; this hypothesis has not been proven and the effect of these findings on humans is unclear at this time. Pancreatic weights following 1 month of iv dosing were similar to weights in rats dosed orally at 18g/m^2 for 3months. In a separate study, intravenous administration of 1.2g/m^2 HPβCD resulted in the decreased concentration of plasma cholesterol; *in vitro* HPβCD has been observed to form an inclusion complex with cholesterol (**Frijlink, H.** et.al., 1991. Pharm.Res. 8:9-16). HpβCD can form inclusion complexes with endogenous substances. As indicated above, cholesterol was decreased 2-fold following 25 months of oral dosing. A significant trend was also observed in adenocarcinoma of the large intestine in HD Γ and adenocarcinoma of the mammary gland in HD E of this same study. None of the above lesions were observed in mice administered the same levels of HPβCD for 2 years.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Mitomycin teratology data as consolidated from the NDA review for Mitomycin C (NDA 50-450), written June, 1972 by S. Bader, Ph.D.:

Segment 2 studies for Mitomycin C were not submitted to the NDA. Data reviewed were taken from NDA 50-443 (Bleomycin) in which Mitomycin reproductive toxicity results were compared with results for Bleomycin.

Wistar rats were administered MMC ip at doses of 0.05, 0.5 and 1.0 mg/kg/day on pregnancy days 6-14. Results included significant increase in number of dead fetuses (MD 0.5mg/kg: 24.6% compared to controls at 8.4%); decrease in mean fetal BW at MD and HD; significant increase in fetal external anomalies (kinked tails, strephexopodia) at all doses (13-30%); fetal skeletal anomalies at all doses (including retardation in ossification of vertebra, phalanges and calcanei); and neonatal anomalies at all doses (hydronephrosis).

ICR-ICL mice were administered MMC ip at doses of 0.05, 0.5, 1.0, and 2.0mg/kg/day on pregnancy days 7-12. Results included lethality and depressed BW (1 and 2mg/kg) of dams at 2mg/kg, significant increase in number of dead fetuses (0.5mg/kg: 20.7%, 2mg/kg: 16.8% compared to controls at 6%); significant dose related decrease in BW of fetuses at 0.5-2.0mg/kg; significant increase in fetal external anomalies at all doses (club foot, kinked tail, cleft palate, maldirection of digits, shortened tail, exencephaly, hydrops, open eye and nanism (8-71% compared to 3% in controls); skeletal anomalies of fetuses at all doses (incomplete ossification of supraoccipital bone, vertebra, calcanei and phalanges); and neonatal anomalies at 0.05mg/kg, the lowest dose tested (retarded testicular, ovarian and uterine growth, dyszoospermia, and closed vagina).

VIII. SPECIAL TOXICOLOGY STUDIES No data submitted.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS

Changes were observed in the kidney, urinary bladder and lungs of rodent and nonrodent species following administration of HPβCD, and single-dose preclinical studies with MME resulted in many similar findings. It thus appears that toxicities due to HPβCD may occur following administration of MME. In addition, carcinogenicity of the pancreas was a result of extended dosing with iv HPβCD in rodents. HPβCD administered orally at 12g/m^2 caused pancreatic lesions in rats. MMC is mutagenic, clastogenic, carcinogenic and teratogenic.

MMC appears to act as a cancer initiator, while HPβCD may act as a cancer promoter, potentially enhancing the effect of MMC. However, additional studies are necessary to substantiate the promoter theory for HPβCD. These studies are beyond the scope of this NDA. There appears to be no valid advantage for the use of MME over the current MMC therapy. In addition, some toxicities observed with MMC (e.g. bladder papillomas and dysplasia following bladder installation) may be enhanced with the effects of HPβCD. However, MME is indicated to be used in patients with advanced or end-stage cancer as palliative therapy after treatment failure. Therefore, the long term effects of the drug are of lesser concern. MitoExtra is approvable based on available clinical and preclinical data on MMC and HPβCD.

X. APPENDIX/ATTACHMENTS

Note: Calculations are based on a clinical dose of 15mg/m^2.

WARNINGS

MitoExtra contains the excipient hydroxypropyl-(beta)-cyclodextrin which produced pancreatic adenocarcinoma in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unclear (See PRECAUTIONS).

Bladder Toxicity

Evidence of bladder toxicities have been observed following single and repeat dose administration of equal to or greater than 0.15g/m^2 and 0.5g/m^2 hydroxypropyl-β-cyclodextrin (HPβCD) excipient of MitoExtra in rodents and dogs, respectively (about 1/60th and 1/20th the amount of HPβCD administered per recommended human dose of MitoExtra on a mg/m^2 basis). Findings included edema, inflammation, cellular inclusions and bladder stones associated with metaplasia; findings persisted at least 3 months following dosing.

Bladder fibrosis/contraction has been reported with intravesical administration (not an approved route of administration), which in rare cases has required cystectomy.

Nephrotoxicity, including irreversible renal necrosis, observed following parenteral administration of HPβCD in rodents and non-rodents appears to be the result of the accumulation and recrystalization of the drug in the proximal tubules of the kidney.

Pregnancy
MitoExtra can cause fetal harm when administered to a pregnant woman. If MitoExtra is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Studies in both mice and rats at doses equal to or greater than 0.5 mg/kg/day (about $1/10^{th}$ and $1/5^{th}$, respectively, the recommended human dose on a mg/m^2 basis), administered intraperitoneally during the period of organogenesis showed that mitomycin C (MMC) significantly decreased numbers of live fetuses; MMC was lethal to dams at 2mg/kg/day in mice. Evidence of fetotoxicity, including delayed fetal development (e.g., depressed fetal body weights, incomplete ossification), fetal external anomalies (e.g., exencephaly, club foot, cleft palate, maldirection of digits, kinked tail), and neonatal anomalies (hydronephrosis, retarded development of reproductive organs) was observed in mice and rats administered doses equal to or greater than 0.05mg/kg/day (about $1/100^{th}$ and $1/50^{th}$, respectively, the recommended human dose on a mg/m^2 basis). In a separate study, MMC was administered to pregnant female mice; offspring exhibited significantly retarded reproductive tract development.

In two separate studies, hydroxypropyl-β-cyclodextrin (HPβCD), the excipient for MitoExtra, was fetotoxic (decreased number of live fetuses, depressed fetal body weight, incomplete ossification) in rats dosed by gavage and intravenously at doses equal to or greater than 50 and 250mg/kg/day, respectively (about $1/30^{th}$ and $1/6^{th}$ the amount of HPβCD administered per recommended human dose of MitoExtra on a mg/m^2 basis).

PRECAUTIONS

Bladder fibrosis/contraction has been reported with intravesical administration (not an approved route of administration), which in rare cases has required cystectomy.
Evidence of bladder toxicities have been observed following single and repeat dose administration of equal to or greater than 0.15g/m^2 and 0.5g/m^2 of the hydroxypropyl-β-cyclodextrin excipient of MitoExtra in rodents and dogs, respectively (about $1/60^{th}$ and $1/20^{th}$ the amount of HPβCD administered per recommended human dose of MitoExtra on a mg/m^2 basis). Findings included edema, inflammation, cellular inclusions and bladder stones associated with metaplasia; findings persisted at least 3 months following dosing.

Carcinogenesis
Mitomycin C is carcinogenic in mice and rats. Three different strains of mice administered intraperitoneal MMC at 0.2ug/mouse (about 1.6 times the recommended human dose on a mg/m^2 basis) twice weekly for 35 doses exhibited increases in undifferentiated sarcomas by study week 40. Likewise, subcutaneous administration of MMC produced undifferentiated sarcomas in two of four mouse strains tested. Following bladder installation in rats, MMC produced bladder papillomas and dysplasia.

Hydroxypropyl-β-cyclodextrin is also carcinogenic in rats. A conventional carcinogenesis study at doses of 500 to 5000mg/kg/day HPβCD (about 1/3rd to 3 times the amount of HPβCD per recommended human dose of MitoExtra on a mg/m^2 basis) administered in the feed for 25 months revealed a significant increase in the incidence of hyperplasia and adenoma and adenocarcinoma of the exocrine pancreas. Similar findings were not observed in the untreated control group and are not reported in historical controls. Development of these tumors may be related to a mitogenic action of cholecystokinin; the clinical relevance of these findings is unclear. A significant trend was also observed in adenocarcinoma of the large intestine and mammary gland of rats of this same study administered 5000mg/kg/day HPβCD (about 3 times the amount of HPβCD per recommended human dose of MitoExtra on a mg/m^2 basis). These findings were not observed in mice administered the same doses of HPβCD for 22-23 months.

Mutagenesis
Mitomycin C is a known mutagen and clastogen. MMC has been shown to be positive in the Ames bacterial mutation assay, chromosomal aberrations assays in mice, Chinese hamsters and human lymphocytes, unscheduled DNA synthesis assay in human lymphocytes, micronucleus test in mice and human lymphocytes and somatic mutation and recombination assays in *Drosophila melanogaster.*

Impairment of Fertility
Intraperitoneal administration of MMC to male mice in a single dose of 5mg/kg (about equal to the recommended human dose on a mg/m^2 basis) or 1mg/kg (about 1/5th the recommended human dose on a mg/m^2 basis) for 5days significantly decreased sperm production, sperm count and sperm motility and resulted in reduced pregnancy rates and an increased frequency of malformations. Doses of 2 and 4mg/kg/day administered intravenously to female mice (about 2/5ths and 4/5ths the recommended human dose on a mg/m^2 basis) inhibited fertilization and implantation.

Pregnancy
Pregnancy Category D (See WARNINGS)

Nursing Mothers
It is not known if mitomycin C is excreted in human milk. Because many drugs are excreted in human milk, women receiving MitoExtra should not breast feed infants (See WARNINGS and PRECAUTIONS.)

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/s/

Margaret Brower
11/8/02 05:04:57 PM
PHARMACOLOGIST

John Leighton
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