CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-120

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

NOV 10 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-120 Submission Date: June 2, 1999

Generic Name:	**Mitoxantrone Concentrate for Injection**
Brand Name:	**NOVANTRONE®**
Indication (s):	**Multiple Sclerosis**
Strength(s):	**10 mL/multidose vial (20 mg)** **12.5 mL/multidose vial (25 mg)** **15 mL/multidose vial (30 mg)**
Formulation:	**Sterile aqueous solution containing mitoxantrone hydrochloride at a concentration equivalent to 2 mg mitoxantrone free base per mL supplied in vials for multidose use**
Sponsor:	**Immunex Corporation** **Seattle, WA**
Type of Submission:	**NDA**
Reviewer:	**Sayed Al-Habet, Ph.D.**
Dates of Review:	**September 10, 1999** **November 1, 1999**

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

SYNOPSIS:

NOVANTRONE (mitoxantrone) is a synthetic antineoplastic anthracenedione for intravenous use. It is a reactive agent that intercalates into DNA through hydrogen bonding, causes crosslinks and strand breaks. It also interferes with RNA and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA.

The drug was initially approved on December 23, 1987 for acute non-lymphocytic leukemia (NDA# 19-297). The sponsor is proposing a new indication for the treatment of patients with secondary progressive multiple sclerosis, including progressive relapsing disease. The proposed recommended dose of Novantrone is 12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months.

viii) —

2. No PK data is available in multiple sclerosis patients, the target population.

B) COMMENT TO THE MEDICAL REVIEWER:

1. Based on the original review of this NDA as well as the autopsy tissue distribution data in humans, the drug appears to bind avidly to the heart tissues for prolong period of time. Therefore, the major safety concern is a possible cardiac toxicity associated with this drug which mimics anthracyclines (e.g., daunorubicin or doxorubicin). This toxicity is believed to be lifetime cumulative and is related to binding of the drug to the myocardium. This is based on the autopsy study discussed in the summary section (Stewart et al, Cancer Treatment Reports vol. No11, November 1986, 1255-126)

2. Since the AUC increased by 3-fold in hepatically impaired patients, from the PK point of view the drug should be administered with caution. It should be noted that the PK data in this study is variable. In addition, the laboratory values were not available to allow adequate dose adjustment in patients with liver impairment. Therefore, the decision has to be made based on the safety and efficacy of the drug at those levels observed in patients with hepatic impairment.

C) COMMENT TO THE SPONSOR:

1. The sponsor has not addressed the deficiencies conveyed in the original NDA# 19-297. In addition, other deficiencies have been identified. Therefore, as Phase IV commitment, the sponsor is requested to provide adequate information to all deficiencies listed above.

2. The sponsor did not provide adequate summary of the individual PK reports and literature. Such summary should be provided in future submissions to facilitate review by the Agency.

D) LABELING COMMENTS:

The sponsor is requested to incorporate the following statement under "Clinical Pharmacology-Drug Interaction/Precautions" section of the label:

1)

2) The results of the hepatic impairment study should be reflected in the Precaution section of the label also.

RECOMMENDATION:

From the PK point of view, this NDA is not acceptable due to the deficiencies listed above (Section A). However, from a clinical point of view the drug will be administered as a short (5-15 minutes) IV infusion once every three months. The safety and efficacy appear to be mainly related to the pharmacodynamic-PD (binding to DNA) rather than the pharmacokinetics-PK behavior of this drug. Therefore, the final assessment of this NDA should be based on additional clinical data to justify the safety and efficacy of the drug.

Please convey the deficiencies and Comments listed in Sections A, C, and D to the sponsor.

TABLE OF CONTENTS

APPEARS THIS WAY
ON ORIGINAL

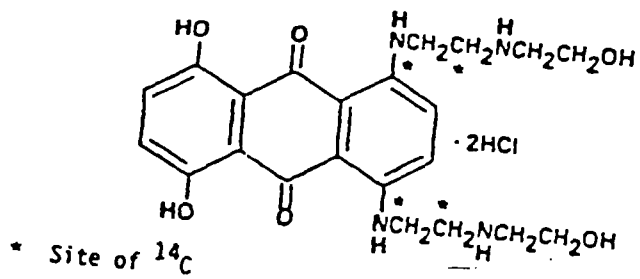
BACKGROUND

Physico-Chemical Properties:

NOVANTRONE is supplied as a concentrate which must be diluted prior to injection. The concentrate is a sterile, nonpyrogenic, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.8% w/v), sodium acetate (0.005 % w/v), acetic acid (0.046% w/v) as inactive ingredients. The solution has a pH of 3.0 to 4.5 and contains 0.14 mEq of sodium per mL. The product does not contain preservatives.

Structural Formula of mitoxantrone:

The molecular weight is 517.41.



APPEARS THIS WAY
ON ORIGINAL

Chemical Formula:

1,4-dihydroxy-5,8-bis [[2-[(2-hydroxyethyl) amino] ethyl]amino]-9,10-anthracenedione dihydrochloride.

Molecular Formula of mitoxantrone: $C_{22}H_{28}N_4O_6 .2HCl$

APPEARS THIS WAY
ON ORIGINAL

Indications and Usage:

[redacted] is being proposed for the treatment of patients with secondary progressive multiple sclerosis, including progressive relapsing disease.

How Supplied:

NOVANTRONE (concentrate for injection) is a sterile aqueous solution containing mitoxantrone hydrochloride at a concentration equivalent to 2 mg mitoxantrone free base per mL supplied in vials for multidose use as follows:

10 mL/mutidose vial (20 mg)
12.5 mL/multidose via (25 mg)
15 mL/mutidose vial (30 mg)

Proposed Dosage and Administration:

The proposed recommended dose of Novantrone is 12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months.

Manufacturer and Manufacturing Site:

NOVANTRONE will be manufactured by Lederles Paranterals, Inc, Carolina, Puerto Rico for Immunex Corporation, Seattle, WA.

SUMMARY REVIEW
OF PHARMACOKINETICS AND BIOAVAILABILITY

Introduction:

The human pharmacokinetic information in this NDA was extracted from NDA# 19-297 in cancer patients and literature reports. A copy of the original PK review for NDA# 19-297 and supplemental review is in Appendices III and IV. It should be noted again that no PK studies were conducted in multiple sclerosis patients.

Pharmacokinetics:

1. The PK of the drug is characterized by a three-compartment system after a single dose in cancer patients.

2. Based on PK studies in cancer patients and several literature reports, the terminal elimination half life is widely variable and ranges from 23 to 215 hours (1-9 days). The wide variability in data is attributed to differences in assays and assay sensitivity, serum handling and storage, coadministration with other drugs, and interindividual variability.

3. It was reported that the drug follows linear PK over a dose range of 15-90mg/m^2. Furthermore, it was observed that there may not be any major changes in the PK of the drug at lower doses of approximately 5-15 mg/m^2 (the range of doses recommended for multiple sclerosis patients). This is based on the previous PK review for NDA# 19-297 dated March 5, 1986 (Appendix III). However, the data are highly variable within and between studies. This could be attributed to several factors namely assay sensitivities, sample size, and patients disease state.

4. No adequate PK information is available following multiple doses.

DISTRIBUTION:

1. Mitoxantrone is 78% bound to plasma proteins at a concentration range of 26-455 ng/mL. The binding is independent of concentration. Also, the plasma protein binding is not affected by the presence of phenytoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin, or aspirin.

2. The volume of distribution is about 1000 L/m^2 which ranges from about 90 to 5000 L/m^2. This shows extensive tissue distribution and binding of the drug.

3. Tissue concentrations of mitoxantrone appear to exceed those in the blood during the terminal phase.

4. Based on biopsy and autopsy data, the drug has been detected in tissues for weeks after administration in humans (Stewart et al, Cancer Treatment Reports vol. No11, November 1986, 1255-126). The data was collected from 11 patients who had received the drug IV, from 10 to 272 days antemortem at doses ranging from 6 to 16 mg/m^2. Mitoxontrone was readily detected in tissues from all patients. Tissue concentrations were proportional to lifetime cumulative dose of mitoxantrone, and decreased very slowly with time. It was also observed that the thyroid, liver, and the heart had the highest concentration of the drug (see Appendix I, Attachments 4-7).

5. Based on both *in vitro* and *in vivo* studies, mitoxantrone binds to erythrocytes, polymorphonuclear leukocytes, monocytes, and platelets in humans.

6. Overall, the tissue distribution in humans appears to be higher than in laboratory animals.

Metabolism/Excretion:

1. Metabolism and elimination of Novantrone are not well characterized.

2. It appears that Novantrone is eliminated primarily through metabolism by the liver and excretion in the bile. However, this information is inconclusive due to the lack of adequate data.

3. Within 5 days of administration, a mean of 10% and 18% of administered radioactivity is eliminated in urine and feces, respectively.

4. Of the material recovered in urine, 65% is unchanged drug and the remaining 35% comprises of a mono-and dicarboxylic acid derivatives and their glucuronides.

5. The carboxylic acid metabolites are not DNA-reactive/cytocidal and their route of formation is unknown.

6. The drug is excreted in milk with a significant concentration of 18 ng/mL for 28 days after the last administration.

Drug Interactions:

- Unknown. No studies have been performed.

- The interaction of mitoxantrone with human P450 system has not been investigated.
- According to the sponsor's labeling, the drug has always been given with corticosteroids in cancer patients. In addition, the drug will also be given with corticosteroids in multiple sclerosis patients. Based on the *in vitro* study, it does not appear that there is interaction with corticosteroids (see 1986 review, Appendix III). However, no formal drug

interaction study was conducted with corticosteroids in humans. Nevertheless, it should be noted that in all clinical trails in this NDA, corticosteroids were coadministered with mitoxantrone. Therefore, we do not know the effect of the presence and/or absence of corticosteroids on the safety and efficacy of mitoxantrone in multiple sclerosis patients. The [redacted] is proposed labeling.

Special Population Studies:

Hepatic Impairment:

- Mitoxantrone clearance is reduced by hepatic impairment.
- The AUC increased by about 3-fold compared to patients with normal liver function.

Renal Impairment:

- No formal study has been performed. However, from the original review (Appendix III), it appears that there are anecdotal reports in some patients with renal impairments. The data were highly variable and inconclusive.
- Considering that the drug will be administered as a single dose once every 3 months and <10% of the drug excreted in urine. Based on this information, the renal guidance indicates that no study needs to be performed, unless clinical concern dictates otherwise.

Age and Gender Effects:

- Unknown. No studies have been performed.

Race:

- Unknown. No studies have been performed.

Pediatric:

- Based on 1986 review (Appendix III), there is one study in pediatric and young patients. The generated PK data were inaccurate and the results were inconclusive.

ClinPharm/Biopharm Briefing on: November 8 . 1999

Reviewed by:

ISL Nov 9, 1999

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

RD/FT initialed by Vijay Tammara, Ph.D. ISL 11/10/99

cc: NDA # 21-120 (Orig.), HFD-120, HFD-860 (Al-Habet, Tammara, Mehta), Biopharm file (Central Document Room)

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 3 PAGE (S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-120 Submission Date: June 2, 1999

Generic Name:	**Mitoxantrone Concentrate for Injection**
Brand Name:	**NOVANTRONE®**
Indication (s):	**Multiple Sclerosis**
Strength(s):	**10 mL/multidose vial (20 mg)** **12.5 mL/multidose vial (25 mg)** **15 mL/multidose vial (30 mg)**
Formulation:	**Sterile aqueous solution containing mitoxantrone hydrochloride at a concentration equivalent to 2 mg mitoxantrone free base per mL supplied in vials for multidose use**
Sponsor:	**Immunex Corporation** **Seattle, WA**
Type of Submission:	**NDA/Labelling Comments**
Reviewer:	**Sayed Al-Habet, Ph.D.**
Dates of Review:	**September 10, 1999** **November 1, 1999**

OCPB review of November 10, 1999 had mentioned several deficiencies as well as Comments that need to be conveyed to the sponsor. In that review, the clinical division was requested to forward them to the sponsor. This review restates the Labeling Comments that were made by OCPB in its review of November 10, 1999. These are as follows:

1) The sponsor is requested to incorporate the following statement under "Clinical Pharmacology-Drug Interaction/Precautions" section of the label:

some antibiotics (e.g., erythromycin, rifampicin, ampicillin, and chloramphenicol).

2) Currently, the Clinical Pharmacology section of the label mentions that mitoxantrone AUC is more than 3-fold higher in patients with severe hepatic impairment than those with normal hepatic function, both groups receiving the same dose. This information should also be mentioned in the Precaution section of the labeling as follows:

[redacted]

3) The Agency will update the labeling for mitoxantrone as the sponsor addresses the pharmacokinetic deficiencies that were conveyed to them, and provides relevant pharmacokinetic information for review.

Please convey Comment #3 to the sponsor.

Reviewed by:

/S/ Feb 22, 2000

APPEARS THIS WAY
ON ORIGINAL

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

RD/FT initialed by Ray Baweja, Ph.D. /S/ 2/22/2000.

cc: NDA # 21-120 (Orig.), HFD-120, HFD-860 (Al-Habet, Baweja, Mehta), Biopharm file (Central Document Room)

APPEARS THIS WAY
ON ORIGINAL

COMPLETED AUG 17 2000

AUG 17 2000 8/18/00

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (OCPB) REVIEW

NDA: **21-120**

Submission Dates: **5/24/00**
7/12/00
7/28/00
8/9/00

OCPB Receipt Dates: **6/2/00**
7/18/00
7/28/00
8/9/00

Drug:	**Novantrone® (Mitoxantrone HCl for injection)**
Strength(s):	**2 mg mitoxantrone free base/ml**
Indication:	**Multiple Sclerosis**
Applicant:	**Immunex**
Type:	***In Vitro* Metabolism Final Reports and Labeling Revisions**
Date of Review:	**8/7/00**
Primary Reviewer:	**Gerald J. Fetterly, Ph.D.**

Background:

Novantrone (mitoxantrone) is a synthetic antineoplastic agent for intravenous use. The drug intercalates into DNA through hydrogen bonding, causes crosslinks and strand breaks, interferes with RNA, and is a potent inhibitor of topoisomerase II. The plasma pharmacokinetics of novantrone is independent of dose, illustrated by fast tissue distribution and slow elimination out of the body. The metabolism of the drug is not well characterized.

Studies with novantrone have suggested that the drug is eliminated primarily through metabolism in the liver and excretion in the bile, but the data is inconclusive. Within 5 days, 10% and 18% of the administered dose is recovered in the urine and feces as parent, mono- and dicarboxylic acid derivatives *via* oxidation, and their glucuronides.

In the March 1, 2000 approvable letter, the Office of Clinical Pharmacology and Biopharmaceutics stated that the metabolism of Novantrone is not well characterized. Due to the introduction of this drug to patients with Multiple Schlerosis, a population significantly different than the ones that receive Novantrone presently, information about the drug's metabolism is needed.

Metabolism and Drug Interaction Issues:

Microsomes:

1. Inhibition Studies:

The sponsor provided *in vitro* data to evaluate the inhibitory potential of mitoxantrone on CYP 450 enzymes. All incubations of microsomes with the parent drug were terminated within 45 min. The results show that mitoxantrone (concentration range: 0.33 – 10 μM) did not cause inhibition of the following enzymes: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 (Tables 1-4). At 100 μM of mitoxantrone, induction of CYP 450 1A2 and 3A4 was observed.

2. Mitoxantrone Metabolism by CYP450s:

The sponsor also provided data to determine the contribution of different CYP450 isoforms to the metabolism of mitoxantrone in human liver microsomes. All incubations of microsomes with the parent drug were terminated within 45 min. At 0.1 and 1 μM concentrations of mitoxantrone, the drug concentration present at the end of the incubation period was greater than the initial concentration for all of the CYP450 isoforms evaluated (Table 5). At 10 μM, the mitoxantrone concentration present at the end of the incubation period was equivalent to the concentration at the start of the experiment. In addition, the concentration of mitoxantrone decreased in the absence of the cofactor. One possible explanation for the unexpected results could be due to the sensitivity of the assay to determine mitoxantrone concentration.

Hepatocytes:

1. Induction Studies:

The potential for mitoxantrone to induce cytochrome P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 activity was investigated using human hepatocytes. Donor 1 was a 43-year old Caucasian male who died from intracranial hemorrhage. The donor had a history of cerebral vascular accident and hypertension. Donor 2 was a 56-year old Caucasian male who died from head trauma. The donor had a history of a benign carpal tumor, was an alcohol consumer, and a heavy smoker. Hepatocytes were isolated according to a two-step collagenase procedure. Cell viability was determined using trypan blue exclusion; only cells with >70% viability were used. After 48 h in culture, the cells were treated with mitoxantrone for 48 h at 0.1, 1, and 10 μM.

No change in CYP 1A2 activity was observed in both donors following 0.1 and 1 μM of mitoxantrone (Table 6). At 10 μM, a 35% induction of activity was observed in donor 1. There was no change in the enzyme activity in donor 2 (heavy smoker), which could be attributed to the enzyme already being induced. The activity of 2A6 was decreased by 19% at 1 μM in donor 1, compared with no measurable activity in donor 2 (Table 6). At 0.1 and 1 μM mitoxantrone, the activity of CYP 2C9 decreased by 24% and 41% in donor 1, respectively (Table 7). At the same concentrations of mitoxantrone, the activity only decreased by 17% in donor 2. The activity of 2C19 decreased by 15%, 26%, and 78% in donor 1 at the mitoxantrone concentrations tested (Table 7). In donor 2, an induction in 2C19 activity was observed at 0.1 and 1 μM of 21% and 57%, respectively. The activity of 2D6 was induced by 22% at 0.1 μM mitoxantrone in donor 1, compared with no change in donor 2 (Table 8). At 0.1 and 1 μM, the activity of 2E1 was induced by 40% and 22% in donor 1 (Table 8). No change in activity was observed in donor 2. The activity of CYP 3A4 was decreased at all concentrations of mitoxantrone (Table 9).

2. Metabolite Identification using LC/MS/MS:

Following the same conditions as above, identification of the metabolites of novantrone was investigated using LC/MS/MS. The spectra in figure 1 represented human hepatocytes with no drug. Figure 2 showed novantrone alone and figure 3

illustrated novantrone with hepatocytes. Four products were identified following incubation of novantrone for 20 h (Fig. 3). The —— spectra revealed peaks present at 8.9, 9.7, 8.8, 11.4, and 11.4 min, with corresponding m/z of 445, 443, 468, 686, and 708, respectively. The peaks at 445 and 443 represented the enol and ketone forms of mitoxantrone. The 468 peak may represent the Na^+-adduct of mitoxantrone. The peaks at 686 and 708 may correspond to the protonated and Na^+-adduct of the mitoxantrone glucuronide conjugate. The sponsor has provided no quantitative data and structural determination of the metabolites.

Comment. –

1. **Clinically, cumulative exposure of mitoxantrone has resulted in high tissue concentrations mainly in the thyroid, liver, and heart. The exposure in the heart especially is important regarding the severe cardiac toxicity associated with anthracyclenes. Thus, the metabolic profile of mitoxantrone may have important implications on the toxicity of the drug and potential drug-drug interactions.**
2. **Based on microsomal data, mitoxantrone does not inhibit CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4.**
3. **The role of various CYP450 isoforms on the metabolism of mitoxantrone are inconclusive based on the results of the microsome studies. In addition, liver enzymes other than CYP450s may be responsible for the metabolic fate of mitoxantrone.**
4. **The results of the hepatocyte studies may suggest that mitoxantrone induces CYP450 2E1.**
5. **The hepatocyte data obtained from donor 2 may have confounded the results of the study since the patient was a heavy smoker and alcoholic.**
6. **The cytotoxic effects of mitoxantrone may explain the decrease in CYP450 activity observed in the hepatocyte studies.**
7. **Following a 20 h incubation of hepatocytes with novantrone, only the parent drug and its glucuronide conjugate were present. A quantitative time course of**

novantrone and its metabolites will give information about the metabolic profile of the parent drug.

Recommendation:

Please forward the comments to the sponsor. Comments 2 and 4 can be included in the labeling for mitoxantrone.

Gerald J. Fetterly, Ph.D. /S/ 8/17/00

RD/FT Initialed by Ray Baweja, Ph.D. /S/ 8/17/00

cc: NDA 21,120, HFD-120, HFD-860 (Mehta, Baweja, Fetterly), Central Document Room (Biopharm File)

Table 1: Phenacetin *O*-deethylase (CYP1A2) and coumarin 7-hydroxylase (CYP2A6) activities in human liver microsomes after administration of test article and corresponding controls

Test/Control Article	Conc. (uM)	Acetaminophen Formation (pmol/mg Protein/min)	Acetaminophen Formation Percent of VC	Total 7-Hydroxycoumarin Formation (pmol/mg Protein/min)	Total 7-Hydroxycoumarin Formation Percent of VC
VC	NA	48.3 ± 1.9	100	145 ± 2	100
FUR	5	33.4 ± 0.9	69.2	NA	NA
TRAN	25	NA	NA	0.00 ± 0.00	0.00
CIC	100	0.00 ± 0.00	NA	0.00 ± 0.00	NA
Mitoxantrone	0.33	43.3 ± 0.7	89.6	143 ± 1	98.6
	1	44.1 ± 0.5	91.3	143 ± 1	98.6
	3.3	45.0 ± 0.9	93.2	144 ± 1	99.3
	10	45.9 ± 0.5	95.0	157 ± 1	108
	100	74.3 ± 0.4	154*	159 ± 1	110

Values are the mean ± standard deviation of N = 3 for experimental groups and CIC, N = 6 for vehicle and positive controls.
Abbreviations: Conc., concentration; VC, vehicle control; NA, not applicable; FUR, furafylline; TRAN, tranylcypromine; CIC, chromatographic interference control.
* At the highest concentration of Mitoxantrone (100 uM), the activity of CYP1A2, phenacetin *O*-deethylation, was 154% of the VC, suggesting that the test article may stimulate the activity of CYP1A2 during 30 min incubation with human liver microsomes.

Table 2: Tolbutamide 4-hydroxylase (CYP2C9) and *S*-mephenytoin 4-hydroxylase (CYP2C19) activities in human liver microsomes after administration of test article and corresponding controls

Test/Control Article	Conc. (uM)	4-OH Tolbutamide Formation (pmol/mg Protein/min)	Percent of VC	4-OH *S*-Mephenytoin Formation (pmol/mg Protein/min)	Percent of VC
VC	NA	70.9 ± 2.1	100	8.24 ± 0.17	100
SULF	50	6.28 ± 0.24	8.86	NA	NA
OME	10	NA	NA	4.41 ± 0.05	53.5
CIC	100	•	NA	0.00 ± 0.00	NA
Mitoxantrone	0.33	67.5 ± 1.9	95.2	8.54 ± 0.10	104
	1	68.2 ± 4.2	96.2	8.40 ± 0.07	102
	3.3	70.6 ± 2.5	99.6	8.32 ± 0.19	101
	10	68.0 ± 0.9	95.9	8.16 ± 0.15	99.0
	100	84.0 ± 1.3	118	8.25 ± 0.14	100

Values are the mean ± standard deviation of N = 3 for experimental groups and CIC, N = 6 for vehicle and positive controls.
Abbreviations: Conc., concentration; 4-OH, 4-hydroxy; VC, vehicle control; NA, not applicable; SULF, sulfaphenazole; OME, omeprazole; CIC, chromatographic interference control.
• The CIC samples were incubated with cofactor instead of Tris Buffer and therefore are invalid. However, no noticeable Test Article interference was observed in any of the samples.

Table 3: Dextromethorphan *O*-demethylase (CYP2D6) and chlorzoxazone 6-hydroxylase (CYP2E1) activities in human liver microsomes after administration of test article and corresponding controls

Test/Control Article	Conc. (uM)	Dextrorphan Formation (pmol/mg Protein/min)	Percent of VC	6-OH Chlorzoxazone Formation (pmol/mg Protein/min)	Percent of VC
VC	NA	42.3 ± 0.3	100	177 ± 5	100
QUIN	1	9.67 ± 0.14	22.9	NA	NA
4-METH	100	NA	NA	27.3 ± 0.5	15.4
CIC	100	0.00 ± 0.00	NA	0.00 ± 0.00	NA
Mitoxantrone	0.33	40.1 ± 1.3	94.8	183 ± 1	103
	1	41.1 ± 0.3	97.2	183 ± 1	103
	3.3	40.8 ± 1.2	96.5	197 ± 9	111
	10	42.2 ± 1.9	99.8	210 ± 1	119
	100	44.7 ± 0.3	106	218 ± 2	123

Values are the mean ± standard deviation of N = 3 for experimental groups and CIC, N = 6 for vehicle and positive controls.
Abbreviations: Conc., concentration; 6-OH, 6-hydroxy; VC, vehicle control; NA, not applicable; QUIN, quinidine; 4-METH, 4-methylpyrazole; CIC, chromatographic interference control.

No. M2000-020

Table 4: Testosterone 6β-hydroxylase (CYP3A4) activities in human liver microsomes after administration of test article and corresponding controls

Test/Control Article	Conc. (uM)	6β-OH Testosterone Formation (pmol/mg Protein/min)	Percent of VC
VC	NA	402 ± 8	100
Ketoconazole	5	33.2 ± 1.1	8.26
CIC	100	0.00 ± 0.00	NA
Mitoxantrone	0.33	394 ± 9	98.0
	1	410 ± 3	102
	3.3	395 ± 10	98.3
	10	421 ± 5	105
	100	820 ± 27	204*

Values are the mean ± standard deviation of N = 3 for experimental groups and CIC, N = 6 for vehicle and positive controls.

Abbreviations: Conc., concentration; 6β-OH, 6β-hydroxy; VC, vehicle control; NA, not applicable; CIC, chromatographic interference control.

* At the highest concentration of Mitoxantrone (100 uM), the activity of CYP3A4, testosterone 6β-hydroxylation, was 204% of the VC, suggesting that the test article may stimulate the activity of CYP3A4 during 10 min incubation with human liver microsomes.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 5 Parent disappearance of mitoxantrone and 7-ethoxycoumarin activities in pooled human microsomes

Controls and Experimental Groups			CYP450 Inhibitor			Cofactor	Mitoxantrone Present	
Group	Name	Conc. (uM)	Isoform	Inhibitor	Conc. (uM)	Presence	Mean	SD
1	Mitoxantrone	0.1	NA	None	NA	Yes	0.795	0.018
2	Mitoxantrone	1	NA	None	NA	Yes	1.43	0.01
3	Mitoxantrone	10	NA	None	NA	Yes	9.96	0.21
4	Mitoxantrone	10	NA	None	NA	No	5.28	0.32
5	7-Ethoxycoumarin	50	NA	None	NA	No	74.2*	11.1
6	NA	NA	NA	None	NA	Yes	0.00	0.00
7	NA	NA	1A2	Furafylline	5	Yes	0.00	0.00
8	NA	NA	2A6	Tranylcypromine	250	Yes	0.00	0.00
9	NA	NA	2C9	Sulfaphenazole	50	Yes	0.00	0.00
10	NA	NA	2C19	Omeprazole	10	Yes	0.00	0.00
11	NA	NA	2D6	Quinidine	1	Yes	0.00	0.00
12	NA	NA	2E1	4-Methylpyrazole	100	Yes	0.00	0.00
13	NA	NA	3A4	Ketoconazole	5	Yes	0.00	0.00
14	Mitoxantrone	0.1	1A2	Furafylline	5	Yes	0.786	0.006
15		1				Yes	1.48	0.02
16		10				Yes	9.88	0.15
17	Mitoxantrone	0.1	2A6	Tranylcypromine	250	Yes	0.794	0.006
18		1				Yes	1.48	0.03
19		10				Yes	9.49	0.77
20	Mitoxantrone	0.1	2C9	Sulfaphenazole	50	Yes	0.812	0.039
21		1				Yes	1.46	0.03
22		10				Yes	9.22	0.23
23	Mitoxantrone	0.1	2C19	Omeprazole	10	Yes	0.788	0.005
24		1				Yes	1.47	0.03
25		10				Yes	9.45	0.30
26	Mitoxantrone	0.1	2D6	Quinidine	1	Yes	0.795	0.007
27		1				Yes	1.50	0.06
28		10				Yes	9.78	0.39
29	Mitoxantrone	0.1	2E1	4-Methylpyrazole	100	Yes	0.798	0.009
30		1				Yes	1.50	0.03
31		10				Yes	8.92	0.25
32	Mitoxantrone	0.1	3A4	Ketoconazole	5	Yes	0.793	0.006
33		1				Yes	1.48	0.06
34		10				Yes	8.71	0.31

Abbreviations: Conc., concentration; SD, standard deviation; NA, not applicable; 1-3, negative controls; 4, metabolic negative control; 5, metabolic positive control; 6, microsomal background control; 7-13, chromatographic interference controls; 14-34, experimental groups.

* Formation of 7-hydroxycoumarin (pmol/mg protein/min).

AUG 29 2000

JW 8/29/00

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (OCPB) REVIEW

NDA: **21-120**

Submission Dates: **5/24/00**
7/12/00
7/21/00
7/28/00
8/9/00

APPEARS THIS WAY ON ORIGINAL

OCPB Receipt Dates: **6/2/00**
7/18/00
7/21/00
7/28/00
8/9/00

Drug:	**Novantrone® (Mitoxantrone HCl for injection)**
Strength(s):	**2 mg mitoxantrone free base/ml**
Indication:	**Multiple Sclerosis**
Applicant:	**Immunex**
Type:	**Labeling Revisions**
Date of Review:	**8/28/00**
Primary Reviewer:	**Gerald J. Fetterly, Ph.D.**

APPEARS THIS WAY ON ORIGINAL

The following statements are the modifications and/or additions to the sponsor's draft labeling of July 21, 2000 on Novantrone from the Office of Clinical Pharmacology and Biopharmaceutics.

Clinical Pharmacology Section.

Metabolism and Elimination.

- Mitoxantrone is excreted in urine and feces as either unchanged drug or as inactive metabolites.

25% was recovered in the feces within 5 days after drug administration. Of the The remaining 35% was composed primarily of monocarboxylic and dicarboxylic acid derivatives and their glucuronide conjugates.

Special Populations

- Geriatric
  - In elderly patients with breast cancer, the systemic mitoxantrone clearance was 21.3 L/hr/m^2, compared with 28.3 L/hr/m^2 and 16.2 L/hr/m^2 for non-elderly patients with nasopharyngeal carcinoma and malignant lymphoma, respectively.
- Hepatic Impairment
  - Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction (bilirubin > 3.4 mg/dL) have an AUC more than three times greater than patients with normal hepatic function receiving the same dose.

- Drug Interactions
  - Pharmacokinetic studies to assess the interaction of NOVANTRONE with concomitantly administered medications have not been performed.

Precautions Section.

- Drug Interactions
  - Mitoxantrone and its metabolites are excreted in bile and urine, but is not known whether the metabolic or excretory pathways are saturable, may be inhibited or induced, or if mitoxantrone and its metabolites undergo enterohepatic circulation.

- Following concurrent administration of NOVANTRONE with corticosteroids, no evidence of drug interactions has been observed.

Special Population

- Hepatic Impairment
  -

Comment.

- In the Gender Special Populations section, "

  The recommendation is to keep the statement; "The effect of gender on mitoxantrone pharmacokinetics is unknown."

Recommendation:

Please forward the additions, modifications, and comment to the sponsor regarding the labeling of Novantrone.

Gerald J. Fetterly, Ph.D. /S/ 8/29/00

RD/FT Initialed by Ray Baweja, Ph.D. /S/ 8/29/00.

cc: NDA 21,120, HFD-120, HFD-860 (Mehta, Baweja, Fetterly), Central Document Room (Biopharm File)