CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19297/S021

APPROVAL LETTER

NDA 19-297/S-021

Immunex Corporation
Attention: Mr. Mark W. Gauthier
Senior Manager, Regulatory Affairs
51 University Street
Seattle, Washington 98101-2936

FEB 04 2000

Dear Mr. Gauthier:

Please refer to your supplemental new drug application dated May 21, 1999, received May 24, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novantrone (mitoxantrone for injection concentrate).

We acknowledge receipt of your submissions dated June 14 and October 8, 1999.

This supplemental new drug application provides for a package insert with the following changes:

1. **ADVERSE REACTIONS** section, **General/Pulmonary** subsection – "Interstitial pneumonitis has been reported in cancer patients receiving combination chemotherapy that included NOVANTRONE."

2. **ADVERSE REACTIONS** section, **General/Cutaneous** – "Extravasation at the infusion suite has been reported, which may result in erythema, swelling, pain, burning, and/or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Plebitis has also been reported at the site of the infusion."

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling submitted on October 8, 1999. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Alvis Dunson, Project Manager, at (301) 594-5767.

Sincerely,

/S/ 2/2/00

Richard Pazdur, M.D.
Director
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19297/S021

FINAL PRINTED LABELING

APPROVED

FEB 4 2000

Labeling: Working Copy

NDA No. 19-297 Rec'd 10-12-99

Reviewed by: A Dunson 2/4/00

at a dose of 0.03 mg/kg (0.02 fold the recommended human dose, on a mg/m² basis), and hepatocellular adenoma in male mice at a dose of 0.1 mg/kg (0.03 fold the recommended human dose, on a mg/m² basis).

Mutagenesis: NOVANTRONE produced a clastogenic effect *in vivo* (rat bone marrow metaphase analysis) and *in vitro* (induced DNA damage in primary rat hepatocytes and SCE in CHO cells), and is mutagenic in bacterial (Ames/Salmonella and E.Coli) and mammalian (L5178Y TK+/- mouse lymphoma) test systems.

Impairment of Fertility: Daily treatment of male rats (71 days prior to, and during the mating period, and until confirmation of pregnancy in females) and female rats (15 days prior to, and during the mating period) with NOVANTRONE I.V. doses up to 0.03 mg/kg (0.02 fold the recommended human dose, on a mg/m² basis) had no effects on fertility.

Drug Interactions: There is no evidence for drug-drug interactions when NOVANTRONE is administered with corticosteroids.

Pregnancy: Pregnancy Category D: (See WARNINGS section.)

Nursing Mothers: NOVANTRONE is excreted in human milk and significant concentrations (18 ng/mL) have been reported for 28 days after the last administration. Because of the potential for serious adverse reactions in infants from NOVANTRONE, breast feeding should be discontinued before starting treatment.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Leukemia - NOVANTRONE has been studied in approximately 800 patients with ANLL. The table below represents the adverse reaction experience in the large U.S. comparative study of mitoxantrone + cytarabine vs daunorubicin + cytarabine. Experience in the large international study was similar. A much wider experience in a variety of other tumor types revealed no additional important reactions other than cardiomyopathy. (See WARNINGS section.) It should be appreciated that the listed adverse reaction categories include overlapping clinical symptoms related to the same condition, e.g., dyspnea, cough and pneumonia. In addition, the listed adverse reactions cannot all necessarily be attributed to chemotherapy as it is often impossible to distinguish effects of the drug and effects of the underlying disease. It is clear, however, that the combination of NOVANTRONE + cytarabine was responsible for nausea and vomiting, alopecia, mucositis/stomatitis, and myelosuppression.

The following table summarizes adverse reactions occurring in patients treated with NOVANTRONE + cytarabine in comparison with those who received daunorubicin + cytarabine for therapy of ANLL. In a large multicenter randomized prospective U.S. trial. Adverse reactions are presented as major categories and selected examples of clinically significant subcategories.

	ALL INDUCTION (percentage of pts entering induction)		ALL CONSOLIDATION (percentage of pts entering consolidation)	
	NOV N=102	DAUN N=102	NOV N=65	DAUN N=69
Cardiovascular	26	28	11	24
CHF	6	6	0	0
Arrhythmias	3	3	4	4
Bleeding	37	41	20	6
GI	16	12	2	2
Petechiae/Ecchymoses	7	9	11	2
Gastrointestinal	89	85	56	61
Nausea/Vomiting	72	67	31	31
Diarrhea	47	47	18	6
Abdominal Pain	15	9	9	4
Mucositis/Stomatitis	20	33	18	8
Hepatic	10	11	14	2
Jaundice	3	8	7	0
Infections	66	73	60	43
UTI	7	2	7	2
Pneumonia	9	7	9	0
Sepsis	34	36	31	18
Fungal Infections	15	13	9	6
Renal Failure	8	6	0	2
Fever	78	71	24	18
Alopecia	37	40	22	16
Pulmonary	43	43	24	14
Cough	13	9	9	2
Dyspnea	18	20	6	0
CNS	30	30	34	35
Seizures	4	4	2	8
Headache	10	9	13	8
Eye	7	8	2	4
Conjunctivitis	5	1	0	0

NOVANTRONE (mitoxantrone for injection concentrate)

Hormone-Refractory Prostate Cancer - Detailed safety information is available for a total of 353 patients with hormone-refractory prostate cancer treated with NOVANTRONE, including 274 patients who received NOVANTRONE in combination with corticosteroids.

The following table summarizes adverse reactions of all grades occurring in ≥ 5% of patients in Trial CCI-NOV22

Adverse Events of Any Intensity Occurring in ≥ 5% of Patients
Trial CCI-NOV22

Event	N+P (n = 80) %	P (n = 61) %
Nausea	61	35
Fatigue	39	14
Alopecia	29	0
Anorexia	25	6
Constipation	16	14
Dyspnea	11	5
Nail bed changes	11	0
Edema	10	4
Systemic Infection	10	7
Mucositis	10	0
UTI	9	4
Emesis	9	5
Pain	8	8
Fever	6	3
Hemorrhage/bruise	6	1
Anemia	5	3
Cough	5	0
Decreased LVEF	5	0
Anxiety/depression	5	3
Dyspepsia	5	5
Skin infection	5	3
Blurred vision	3	5

No non-hematologic adverse events of Grade 3/4 were seen in > 5% of patients.

The next table summarizes adverse events of all grades occurring in ≥ 5% of patients in Trial CALGB 9182.

Adverse Events of Any Intensity Occurring in ≥ 5% of Patients
Trial CALGB 9182

Event	M+H (n = 112) n	%	M (n = 113) n	%
Decreased WBC	86	87	4	4
Granulocytes/bands	88	79	9	8
Decreased hemoglobin	83	75	42	39
Lymphocytes	76	72	27	25
Pain	45	41	44	39
Platelets	43	39	8	7
Alkaline Phosphatase	41	37	42	38
Malaise/fatigue	37	34	16	14
Hyperglycemia	33	31	32	30
Edema	31	30	15	14
Nausea	28	26	9	8
Anorexia	24	22	16	14
BUN	24	22	22	20
Transaminase	22	20	16	14
Alopecia	20	20	1	1
Cardiac function	19	18	0	0
Infection	18	17	4	4
Weight loss	18	17	13	12
Dyspnea	16	15	9	8
Diarrhea	16	14	4	4
Fever in absence of infection	15	14	7	6
Weight gain	15	14	16	15
Creatinine	14	13	11	10
Other gastrointestinal	13	14	11	11
Vomiting	12	11	6	5
Other neurologic	11	11	5	5
Hypocalcemia	10	10	5	5
Hematuria	9	11	5	6
Hyponatremia	9	9	3	3
Sweats	9	9	2	2
Other liver	8	8	8	8
Stomatitis	8	8	1	1
Cardiac dysrhythmia	7	7	3	3

NOVANTRONE (mitoxantrone for injection concentrate)

Hypokalemia	7	7	4	4
Neuro/constipation	7	7	2	2
Neuro/motor	7	7	3	3
Neuro/mood	6	6	2	2
Skin	6	6	4	4
Cardiac ischemia	5	5	1	1
Chills	5	5	0	0
Hemorrhage	5	5	3	3
Myalgias/arthralgias	5	5	3	3
Other kidney/bladder	5	5	3	3
Other endocrine	5	5	3	4
Other pulmonary	5	5	3	3
Hypertension	4	4	5	5
Impotence/libido	4	7	2	3
Proteinuria	4	6	2	3
Sterility	3	5	2	3

General

Allergic Reaction: Hypotension, urticaria, dyspnea, and rashes have been reported occasionally.

Cutaneous: Extravasation at the infusion site has been reported, which may result in erythema, swelling, pain, burning, and/or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Phlebitis has also been reported at the site of infusion.

Hematologic: Topoisomerase II inhibitors, including NOVANTRONE, in combination with other antineoplastic agents, have been associated with the development of acute leukemia.

Leukemia - Myelosuppression is rapid in onset and is consistent with the requirement to produce significant marrow hypoplasia in order to achieve a response in acute leukemia. The incidences of infection and bleeding seen in the U.S. trial are consistent with those reported for other standard induction regimens.

Hormone-refractory prostate cancer - In a randomized study where dose escalation was required for nadir neutrophil counts greater than 1000/mm³, Grade 4 neutropenia (ANC < 500 /mm³) was observed in 64% of patients treated with NOVANTRONE + low-dose prednisone. In a separate randomized trial where patients were treated with 14 mg/m², Grade 4 neutropenia in 23% of patients treated with NOVANTRONE + hydrocortisone was observed. Neutropenic fever/infection occurred in 11% and 10% of patients receiving NOVANTRONE + corticosteroids, respectively, on the two trials. Platelets < 50,000/mm³ were noted in 4% and 3% of patients receiving NOVANTRONE + corticosteroids on these trials, and there was one patient death on NOVANTRONE + hydrocortisone due to intracranial hemorrhage after a fall.

Gastrointestinal: Nausea and vomiting occurred acutely in most patients and may have contributed to reports of dehydration, but were generally mild to moderate and could be controlled through the use of antiemetics. Stomatitis/mucositis occurred within 1 week of therapy.

Cardiovascular: Congestive heart failure, tachycardia, EKG changes including arrhythmias, chest pain, and asymptomatic decreases in left ventricular ejection fraction have occurred. (See WARNINGS section.)

Pulmonary: Interstitial pneumonitis has been reported in cancer patients receiving combination chemotherapy that included NOVANTRONE.

OVERDOSAGE

There is no known specific antidote for NOVANTRONE. Accidental overdoses have been reported. Four patients receiving 140 - 180 mg/m² as a single bolus injection died as a result of severe leukopenia with infection. Hematologic support and antimicrobial therapy may be required during prolonged periods of medullary hypoplasia.

Although patients with severe renal failure have not been studied, NOVANTRONE is extensively tissue bound and it is unlikely that the therapeutic effect or toxicity would be mitigated by peritoneal or hemodialysis.

DOSAGE AND ADMINISTRATION (See WARNINGS section.)

Hormone-Refractory Prostate Cancer: Based on data from two Phase III comparative trials of NOVANTRONE plus corticosteroids versus corticosteroids alone, the recommended dosage of NOVANTRONE is 12 to 14 mg/m² given as a short intravenous infusion every 21 days.

Combination Initial Therapy for ANLL in Adults: For induction, the recommended dosage is 12 mg/m² of NOVANTRONE daily on days 1-3 given as an intravenous infusion, and 100 mg/m² of cytarabine for 7 days given as a continuous 24-hour infusion on days 1-7.

Most complete remissions will occur following the initial course of induction therapy. In the event of an incomplete antileukemic response, a second induction course may be given. NOVANTRONE should be given for 2 days and cytarabine for 5 days using the same daily dosage levels.

If severe or life-threatening nonhematologic toxicity is observed during the first induction course, the second induction course should be withheld until toxicity clears.

Consolidation therapy which was used in 2 large randomized multicenter trials consisted of NOVANTRONE, 12 mg/m² given by intravenous infusion daily on days 1 and 2 and cytarabine, 100 mg/m² for 5 days given as a continuous 24-hour infusion on days 1-5. The first course was given approximately 6 weeks after the final induction course, the second was generally administered 4 weeks after the first. Severe myelosuppression occurred. (See CLINICAL PHARMACOLOGY section.)

Hepatic Impairment: For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations. (See CLINICAL PHARMACOLOGY, Special Populations: *Hepatic Impairment.*)

NOVANTRON

Preparation and Administration Pr
MUST BE DILUTED PRIOR TO USE
Parenteral drug products should be i
coloration prior to administration whe
The dose of NOVANTRONE should b
Sodium Chloride Injection (USP) or 5
may be further diluted into Dextrose
with Normal Saline and used immedi
NOVANTRONE should not be mixed
tate may form. Because specific com
mended that NOVANTRONE not be r
The diluted solution should be introd
intravenous infusion of 0.9% Sodium
Injection (USP) over a period of not l
immediately in an appropriate bolus
the remaining portion of the undilute
days between 15°-25° C (59°-77° F)
PRESERVATIVE.
If extravasation occurs, the administra
vein. The nonvesicant properties of N
following extravasation. However, ca
to avoid contact of NOVANTRONE w
Skin accidentally exposed to NOVAN
eyes are involved, standard irrigation
gloves, and protective gowns is reco
Procedures for proper handling and d
lines on this subject have been publis
recommended in the guidelines are n

REFERENCES

1. Recommendations for the Safe Ha
2621. For sale by the Superintendent
20402.
2. AMA Council Report. Guidelines fo
253 (11):1500-1502.
3. National Study Commission on Cyt
Agents. Available from Louis P. Jeffre
Exposure, Massachusetts College of
Boston, Massachusetts 02115.
4. Clinical Oncological Society of Aus
neoplastic agents. *Med J Australia*. 1
5. Jones RB, et al. Safe handling of c
Center. *Cancer - A Cancer Journal for Cli*
6. American Society of Hospital Phar
hazardous drugs. *Am J Hosp Pharm*.
7. OSHA Work-Practice guidelines fo
Am J Hosp Pharm. 1986; 43:1193-12

HOW SUPPLIED

NOVANTRONE® (mitoxantrone for inje
antrone hydrochloride at a concentrat
vials for multidose use as follows:

NDC 66406-640-03 - 10 mL/v
NDC 66406-640-05 - 12.5 mL
NDC 66406-640-07 - 15 mL/v

NOVANTRONE® (mitoxantrone for inje
stored between 15°-25°C
(59°-77°F). DO NOT FREEZE.

Manufactured for IMMUNEX CORPOR
by LEDERLE PARENTERALS, INC., C

Rev 0166-06
Revised 10/99

DWG. 5312 3-5-96 BACK

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...arabine for therapy of ANLL in a
...are presented as major cate-

ALL CONSOLIDATION
(percentage of pts entering consolidation)

MOV N=55	DAUN N=59
11	24
0	0
4	4
20	6
2	2
11	2
58	51
31	31
15	8
8	4
15	6
14	2
7	0
60	43
7	2
9	0
31	18
8	6
0	2
24	18
22	16
24	14
9	2
6	0
34	35
2	8
13	8
2	4
0	0

NOVANTRONE (mitoxantrone for injection concentrate)

Hormone-Refractory Prostate Cancer - Detailed safety information is available for a total of 353 patients with hormone-refractory prostate cancer treated with NOVANTRONE, including 274 patients who received NOVANTRONE in combination with corticosteroids.

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Anorexia	25	6
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Edema	10	4
Systemic infection	10	7
Mucositis	10	0
UTI	9	4
Emesis	9	6
Pain	8	8
Fever	8	3
Hemorrhage/bruise	8	1
Anemia	6	3
Cough	6	0
Decreased LVEF	5	0
Anxiety/depression	5	3
Dyspepsia	5	6
Skin infection	5	3
Blurred vision	3	0

No non-hematologic adverse events of Grade 3/4 were seen in > 5% of patients.

The next table summarizes adverse events of all grades occurring in ≥ 5% of patients in Trial CALGB 9182.

Adverse Events of Any Intensity Occurring in ≥ 5% of Patients
Trial CALGB 9182

Event	M+H (n = 112) n	M+H (n = 112) %	H (n = 113) n	H (n = 113) %
Decreased WBC	96	87	4	4
Granulocytes/bands	88	79	3	3
Decreased hemoglobin	83	75	42	39
Lymphocytes	78	72	27	25
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Creatinine	14	13	11	10
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Hypokalemia	7	7	4	4
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Skin	6	6	4	4
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Chills	5	5	0	0
Hemorrhage	5	5	3	3
Myalgias/arthralgias	5	5	3	3
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Hepatic Impairment: For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations. (See CLINICAL PHARMACOLOGY, Special Populations: *Hepatic Impairment.*)

NOVANTRONE (mitoxantrone for injection concentrate)

Preparation and Administration Precautions: NOVANTRONE CONCENTRATE MUST BE DILUTED PRIOR TO USE.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The dose of NOVANTRONE should be diluted to at least 50 mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). NOVANTRONE may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately. DO NOT FREEZE.

NOVANTRONE should not be mixed in the same infusion as heparin since a precipitate may form. Because specific compatibility data are not available, it is recommended that NOVANTRONE not be mixed in the same infusion with other drugs. The diluted solution should be introduced slowly into the tubing as a freely running intravenous infusion of 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP) over a period of not less than 3 minutes. Unused infusion solutions should be discarded immediately in an appropriate fashion. In the case of multidose use, after penetration of the stopper, the remaining portion of the undiluted NOVANTRONE concentrate should be stored not longer than 7 days between 15°-25° C (59°-77° F) or 14 days under refrigeration. DO NOT FREEZE. CONTAINS NO PRESERVATIVE.

If extravasation occurs, the administration should be stopped immediately and restarted in another vein. The nonvesicant properties of NOVANTRONE minimize the possibility of severe local reactions following extravasation. However, care should be taken to avoid extravasation at the infusion site and to avoid contact of NOVANTRONE with the skin, mucous membranes or eyes.

Skin accidentally exposed to NOVANTRONE should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA.* 1985; 253 (11) :1590-1592.

3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia.* 1983; 1:426-428.

5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *Ca - A Cancer Journal for Clinicians.* Sept/Oct 1983; 258-263.

6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990; 47:1033-1049.

7. OSHA Work-Practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. *Am J Hosp Pharm.* 1986; 43:1193-1204.

HOW SUPPLIED

NOVANTRONE® (mitoxantrone for injection concentrate) 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:

NDC 59408-640-03 - 10 mL/multidose vial (20 mg)
NDC 59408-640-05 - 12.5 mL/multidose vial (25 mg)
NDC 59408-640-07 - 15 mL/multidose vial (30 mg)

NOVANTRONE® (mitoxantrone for injection concentrate) should be stored between 15°-25°C (59°-77°F). DO NOT FREEZE.

immunex®

Manufactured for IMMUNEX CORPORATION, Seattle, WA 98101 by LEDERLE PARENTERALS, INC., Carolina, Puerto Rico 00987

Rev 0196-08
Revised 10/99

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NOVANTRONE®

mitoxantrone

for injection concentrate

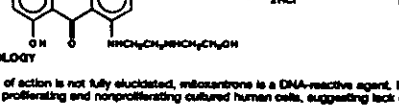
WARNING

NOVANTRONE® (mitoxantrone for injection concentrate) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Except for the treatment of acute nonlymphocytic leukemia, NOVANTRONE® therapy generally should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving NOVANTRONE®.

DESCRIPTION

NOVANTRONE® (mitoxantrone hydrochloride) is a synthetic antineoplastic anthracenedione for intravenous use. The molecular formula is $C_{22}H_{28}N_4O_6 \cdot 2HCl$ and the molecular weight is 517.41. It 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 (0.80% w/v), sodium acetate (0.005% w/v), and 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. The chemical name is 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl) amino]ethyl]amino]-9,10-anthracenedione dihydrochloride and the structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Although its mechanism of action is not fully elucidated, mitoxantrone is a DNA-reactive agent. It has a cytocidal effect on both proliferating and nonproliferating cultured human cells, suggesting lack of cell cycle phase specificity.

Pharmacokinetics

Pharmacokinetics of mitoxantrone in patients following a single intravenous administration of NOVANTRONE can be characterized by a three-compartment model. The mean alpha half-life of mitoxantrone is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours and the mean gamma (terminal or elimination) half-life is 23 to 215 hours (median approximately 75 hours). Pharmacokinetic studies have not been performed in humans receiving multiple daily dosing. Distribution to tissues is extensive; steady-state volume of distribution exceeds 1,000 L/m2. Tissue concentrations of mitoxantrone appear to exceed those in the blood during the terminal elimination phase. In the monkey, distribution to brain, spinal cord, eye, and spinal fluid is low.

In patients administered 15-80 mg/m² of NOVANTRONE intravenously, there is a linear relationship between dose and the area under the concentration-time curve.

Mitoxantrone is 78% bound to plasma proteins in the observed concentration range of 26-455 ng/mL. This binding is independent of concentration and is not affected by the presence of phenytoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin, or aspirin.

Metabolism and Elimination: Metabolism and elimination of mitoxantrone following NOVANTRONE administration are not well characterized. Eleven percent or less of mitoxantrone is recovered in the urine, and 25% or less is recovered in the feces, within five days after drug administration. Of the

material recovered in the urine, 65% is unchanged drug. The remaining 35% is comprised primarily of a mono- and a dicarboxylic acid derivative and their glucuronide conjugates. These carboxylic acid metabolites are not DNA-reactive/cytocidal, and their route of formation is unknown.

Special Populations:

Gender: The effect of gender on mitoxantrone pharmacokinetics is unknown.

Geriatric: Mitoxantrone pharmacokinetics in the elderly are unknown.

Pediatric: Mitoxantrone pharmacokinetics in the pediatric population are unknown.

Race: The effect of race on mitoxantrone pharmacokinetics is unknown.

Renal Impairment: Mitoxantrone pharmacokinetics in patients with renal impairment are unknown.

Hepatic Impairment: Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction (bilirubin greater than 3.4 mg/dL) have an AUC more than 3-fold that of patients with normal hepatic function receiving the same dose. For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations.

Drug Interactions: Pharmacokinetic studies of the interaction of NOVANTRONE with concomitantly administered medications have not been performed. The interaction of mitoxantrone with the human P450 system has not been investigated.

Clinical Trials

Advanced Hormone-Refractory Prostate Cancer

A multicenter phase 2 trial of NOVANTRONE and low-dose prednisone (N + P) was conducted in 27 symptomatic patients with hormone-refractory prostate cancer. Using NPCP (National Prostate Cancer Project) criteria for disease response, there was one partial responder and 12 patients with stable disease. However, nine patients or 33% achieved a palliative response defined on the basis of reduction in analgesic use or pain intensity.

These findings lead to the initiation of a randomized multicenter trial (CCI-NOV22) comparing the effectiveness of (N + P) to low-dose prednisone alone (P). Eligible patients were required to have metastatic or locally advanced disease that had progressed on standard hormonal therapy, a castrate serum testosterone level, and at least mild pain at study entry. NOVANTRONE was administered at a dose of 12 mg/m² by short IV infusion every three weeks. Prednisone was administered orally at a dose of 5 mg twice a day. Patients randomized to the prednisone arm were crossed over to the N + P arm if they progressed or if they were not improved after a minimum of six weeks of therapy with prednisone alone.

A total of 161 patients were randomized, 80 to the N + P arm and 81 to the P arm. The median NOVANTRONE dose administered was 12 mg/m² per cycle. The median cumulative NOVANTRONE dose administered was 73 mg/m² (range of 12 to 212 mg/m²).

A primary palliative response (defined as a 2-point decrease in pain intensity in a 6-point pain scale, associated with stable analgesic use, and lasting a minimum of 6 weeks) was achieved in 29% of patients randomized to N + P compared to 12% of patients randomized to P alone ($p = 0.011$). Two responders left the study after meeting primary response criterion for two consecutive cycles. For the purposes of this analysis, these two patients were assigned a response duration of zero days. A secondary palliative response was defined as a 50% or greater decrease in analgesic use, associated with stable pain intensity, and lasting a minimum of 6 weeks. An overall palliative response (defined as primary plus secondary responses) was achieved in 38% of patients randomized to N + P compared to 21% of patients randomized to P ($p = 0.025$).

The median duration of primary palliative response for patients randomized to N + P was 7.6 months compared to 2.1 months for patients randomized to P alone ($p = 0.0009$). The median duration of overall palliative response for patients randomized to N + P was 5.6 months compared to 1.9 months for patients randomized to P alone ($p = 0.0004$).

Time to progression was defined as a 1-point increase in pain intensity, or a >25% increase in analgesic use, or evidence of disease progression on radiographic studies, or requirement for radiotherapy. The median time to progression for all patients randomized to N + P was 4.4 months compared to 2.3 months for all patients randomized to P alone ($p = 0.0001$). Median time to death was 11.3 months for all patients on the N + P arm compared to 10.8 months for all patients on P alone ($p = 0.2334$).

Forty-eight patients on the P arm crossed over to receive N + P. Of these, thirty patients had progressed on P, while 18 had stable disease on P. The median cycle of crossover was 6 cycles (range of 2 to 16 cycles). Time trends for pain intensity prior to crossover were significantly worse for patients who crossed over than for those who remained on P alone ($p = 0.012$). Nine patients (19%) demonstrated a palliative response on N + P after crossover. The median time to death for patients who crossed over to N + P was 12.7 months.

The clinical significance of a fall in prostate specific antigen (PSA) concentrations after chemotherapy is unclear. On the CCI-NOV22 trial, a PSA fall of 50% or greater for two consecutive follow-up assessments after baseline was reported in 33% of all patients randomized to the N + P arm and 9% of all patients randomized to the P arm. These findings should be interpreted with caution since PSA responses were not defined prospectively. A number of patients were inevaluable for response, and there was an imbalance between treatment arms in the number of evaluable patients. In addition, PSA reduction did not correlate precisely with palliative response, the primary efficacy endpoint of this study. For example, among the 26 evaluable patients randomized to the N + P arm who had a ≥ 80% reduction in PSA, only 13 had a primary palliative response. Also, among 42 evaluable patients on this arm who did not have this reduction in PSA, 8 nonetheless had a primary palliative response.

Investigators at Cancer and Leukemia Group B (CALGB) conducted a phase III comparative trial of NOVANTRONE plus hydrocortisone (N + H) versus hydrocortisone alone (H) in patients with hormone-refractory prostate cancer (CALGB 9182). Eligible patients were required to have metastatic disease that had progressed despite at least one hormonal therapy. Progression at study entry was defined on

the basis of progressive symptoms, increases in measurable or osseous disease, or rising PSA levels. NOVANTRONE was administered intravenously at a dose of 14 mg/m² every 21 days and hydrocortisone was administered orally at a daily dose of 40 mg. A total of 242 subjects were randomized, 119 to the N + H arm and 123 to the H arm. There were no differences in survival between the two arms, with a median of 11.1 months in the N + H arm, and 12 months in the H arm ($p = 0.3298$).

Using NPCP criteria for response, partial response were achieved in 10 patients (8.4%) randomized to the N + H arm compared with 2 patients (1.6%) randomized to the H arm ($p = 0.018$). The median time to progression, defined by NPCP criteria, for patients randomized to the N + H arm was 7.3 months compared to 4.1 months for patients randomized to H alone ($p = 0.0654$).

Approximately 60% of patients on each arm required analgesics at baseline. Analgesic use was measured in this study using a 6-point scale. The best percent change from baseline in mean analgesic use was -17% for 61 patients with available data on the N + H arm, compared with +17% for 61 patients on H alone ($p = 0.014$). A time trend analysis for analgesic use in individual patients also showed a trend favoring the N + H arm over H alone but was not statistically significant.

Pain intensity was measured using the Symptom Distress Scale (SDS) Pain Item 2 (a 6-point scale). The best percent change from baseline in mean pain intensity was -14% for 37 patients with available data on the N + H arm, compared with +8% for 38 patients on H alone ($p = 0.057$). A time trend analysis for pain intensity in individual patients showed no difference between treatment arms.

Acute Nonlymphocytic Leukemia

In two large randomized multicenter trials, remission induction therapy for acute nonlymphocytic leukemia (ANLL) with NOVANTRONE 12 mg/m² daily for 3 days as a 10-minute intravenous infusion and cytarabine 100 mg/m² for 7 days given as a continuous 24-hour infusion was compared with daunorubicin 45 mg/m² daily by intravenous infusion for 3 days plus the same dose and schedule of cytarabine used with NOVANTRONE. Patients who had an incomplete antileukemic response received a second induction course in which NOVANTRONE or daunorubicin was administered for 2 days and cytarabine for 5 days using the same daily dosage schedule. Response rates and median survival information for both the U.S. and International multicenter trials are given in the following table:

Trial	% Complete Response (CR)		Median Time to CR (days)		Median Survival (days)	
	NOV	DAUN	NOV	DAUN	NOV	DAUN
U.S.	63 (62/98)	53 (54/102)	35	42	312	237
International	50 (56/112)	51 (62/123)	36	42	192	230

NOV = NOVANTRONE® + cytarabine

DAUN = daunorubicin + cytarabine

In these studies, two consolidation courses were administered to complete responders on each arm. Consolidation therapy consisted of the same drug and daily dosage used for remission induction, but only 5 days of cytarabine and 2 days of NOVANTRONE or daunorubicin were given. The first consolidation course was administered 6 weeks after the start of the final induction course if the patient achieved a complete remission. The second consolidation course was generally administered 4 weeks later. Full hematologic recovery was necessary for patients to receive consolidation therapy. For the U.S. trial, median granulocyte nadirs for patients receiving NOVANTRONE + cytarabine for consolidation courses 1 and 2 were 1000/mm³ for both courses, and for those patients receiving daunorubicin + cytarabine nadirs were 1700/mm³ and 2000/mm³, respectively. Median platelet nadirs for patients who received NOVANTRONE + cytarabine for consolidation courses 1 and 2 were 17,000/mm³ and 14,000/mm³, respectively, and were 33,000/mm³ and 22,000/mm³ in courses 1 and 2 for those patients who received daunorubicin + cytarabine. The benefit of consolidation therapy in ANLL patients who achieve a complete remission remains controversial. However, in the only well-controlled prospective, randomized multicenter trials with NOVANTRONE in ANLL, consolidation therapy was given to all patients who achieved a complete remission. During consolidation in the U.S. study, two myelosuppression-related deaths occurred on the NOVANTRONE arm and one on the daunorubicin arm. However, in the International study there were eight deaths on the NOVANTRONE arm during consolidation which were related to the myelosuppression and none on the daunorubicin arm where less myelosuppression occurred.

INDICATIONS AND USAGE

NOVANTRONE in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.

NOVANTRONE in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias.

CONTRAINDICATIONS

NOVANTRONE is contraindicated in patients who have demonstrated prior hypersensitivity to it.

WARNINGS

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medullary suppression.

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Safety for use by routes other than i

NOVANTRONE is not indicated for i
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NOVANTRONE should not be given
including paralysis and bowel and b

Pregnancy - NOVANTRONE may ca
rats, at doses of ≥0.1 mg/kg (0.05 t
weight and retarded development o
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mended human dose on a mg/m² ba
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patient becomes pregnant while tak
to the fetus. Women of childbearing

Topoisomerase II inhibitors, includin
have been associated with the deve

Cardiac Effects

Because of the possible danger of c
doxorubicin, the benefit-to-risk ratio
before starting therapy.

General - Functional cardiac change
irreversible congestive heart failure c
mon in patients with prior treatment
ing cardiovascular disease. Such pa
ation of therapy. In investigational tri
received up to the cumulative dose c
tive heart failure. The overall cumulat
this dose was 13% in comparative tr

Leukemia - Acute congestive heart fa
NOVANTRONE for ANLL. In first-line
+ cytarabine in adult patients with pr
heart failure in 6.5% of patients on
effects is difficult to establish in this
anemia, fever and infection, and hem

Hormone-Refractory Prostate Cancer
pestive heart failure may occur in pa
NOVANTRONE. In a randomized con
dose prednisone, 7 of 128 patients (
any decrease in LVEF below the norm
Two patients had a prior history of c
patients with cardiac effects ranged f

Among 112 patients evaluable for sa
trial, 18 patients (16%) had a reductio
patients (2%) experienced pulmonary
these patients is not available.

PRECAUTIONS

General: Therapy with NOVANTRON
hematologic and chemical laboratory

Systemic infections should be treate
NOVANTRONE.

Information for Patients: NOVANTR
administration, and patients should b
sclera may also occur. Patients shou

Laboratory Tests: Serial complete b
dose adjustments. (See DOSAGE AN

In leukemia treatment, hyperuricemia
NOVANTRONE. Serum uric acid leve
the initiation of antileukemic therapy.

Carcinogenesis, Mutagenesis, Imp

Carcinogenesis: Intravenous treatme
NOVANTRONE resulted in an increa

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A primary palliative response (defined as a 2-point decrease in pain intensity in a 6-point pain scale, associated with stable analgesic use, and lasting a minimum of 6 weeks) was achieved in 29% of patients randomized to N + P compared to 12% of patients randomized to P alone (p = 0.011). Two responders left the study after meeting primary response criterion for two consecutive cycles. For the purposes of this analysis, these two patients were assigned a response duration of zero days. A secondary palliative response was defined as a 50% or greater decrease in analgesic use, associated with stable pain intensity, and lasting a minimum of 6 weeks. An overall palliative response (defined as primary plus secondary responses) was achieved in 39% of patients randomized to N + P compared to 21% of patients randomized to P (p = 0.025).

The median duration of primary palliative response for patients randomized to N + P was 7.6 months compared to 2.1 months for patients randomized to P alone (p = 0.0008). The median duration of overall palliative response for patients randomized to N + P was 6.6 months compared to 1.8 months for patients randomized to P alone (p = 0.0004).

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Patients with preexisting myelosuppression as the result of prior drug therapy should not receive NOVANTRONE unless it is felt that the possible benefit from such treatment warrants the risk of further medullary suppression.

The safety of NOVANTRONE in patients with hepatic insufficiency is not established. (See CLINICAL PHARMACOLOGY section.)

Safety for use by routes other than intravenous administration has not been established.

NOVANTRONE is not indicated for intra-arterial injection. There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection.

NOVANTRONE should not be given by intrathecal injection. There have been reports of neuropathy including paralysis and bowel and bladder dysfunction following intrathecal injection.

Pregnancy - NOVANTRONE may cause fetal harm when administered to a pregnant woman. In treated rats, at doses of ≥0.1 mg/kg (0.05 fold the recommended human dose on a mg/m² basis) low fetal birth weight and retarded development of the fetal kidney were seen in greater frequency. In treated rabbits, an increased incidence of premature delivery was observed at doses ≥0.01 mg/kg (0.01 fold the recommended human dose on a mg/m² basis). NOVANTRONE was not teratogenic in rabbits. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Topoisomerase II Inhibitors, including NOVANTRONE, in combination with other antineoplastic agents, have been associated with the development of acute leukemia.

Cardiac Effects

Because of the possible danger of cardiac effects in patients previously treated with daunorubicin or doxorubicin, the benefit-to-risk ratio of NOVANTRONE therapy in such patients should be determined before starting therapy.

General - Functional cardiac changes including decreases in left ventricular ejection fraction (LVEF) and irreversible congestive heart failure can occur with NOVANTRONE. Cardiac toxicity may be more common in patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease. Such patients should have regular cardiac monitoring of LVEF from the initiation of therapy. In investigational trials of intermittent single doses in other tumor types, patients who received up to the cumulative dose of 140 mg/m² had a cumulative 2.6% probability of clinical congestive heart failure. The overall cumulative probability rate of moderate or serious decreases in LVEF at this dose was 13% in comparative trials.

Leukemia - Acute congestive heart failure may occasionally occur in patients treated with NOVANTRONE for ANLL. In first-line comparative trials of NOVANTRONE + cytarabine vs daunorubicin + cytarabine in adult patients with previously untreated ANLL, therapy was associated with congestive heart failure in 6.5% of patients on each arm. A causal relationship between drug therapy and cardiac effects is difficult to establish in this setting since myocardial function is frequently depressed by the anemia, fever and infection, and hemorrhage which often accompany the underlying disease.

Hormone-Refractory Prostate Cancer - Functional cardiac changes such as decreases in LVEF and congestive heart failure may occur in patients with hormone-refractory prostate cancer treated with NOVANTRONE. In a randomized comparative trial of NOVANTRONE plus low-dose prednisone vs low-dose prednisone, 7 of 128 patients (5.5 %) treated with NOVANTRONE had a cardiac event defined as any decrease in LVEF below the normal range, congestive heart failure (n = 3), or myocardial ischemia. Two patients had a prior history of cardiac disease. The total NOVANTRONE dose administered to patients with cardiac effects ranged from >48 to 212 mg/m².

Among 112 patients evaluable for safety on the NOVANTRONE + hydrocortisone arm of the CALGB trial, 18 patients (19%) had a reduction in cardiac function, 8 patients (5%) had cardiac ischemia, and 2 patients (2%) experienced pulmonary edema. The range of total NOVANTRONE doses administered to these patients is not available.

PRECAUTIONS

General: Therapy with NOVANTRONE should be accompanied by close and frequent monitoring of hematologic and chemical laboratory parameters, as well as frequent patient observation.

Systemic infections should be treated concomitantly with or just prior to commencing therapy with NOVANTRONE.

Information for Patients: NOVANTRONE may impart a blue-green color to the urine for 24 hours after administration, and patients should be advised to expect this during therapy. Bluish discoloration of the sclera may also occur. Patients should be advised of the signs and symptoms of myelosuppression.

Laboratory Tests: Serial complete blood counts and liver function tests are necessary for appropriate dose adjustments. (See DOSAGE AND ADMINISTRATION section.)

In leukemia treatment, hyperuricemia may occur as a result of rapid lysis of tumor cells by NOVANTRONE. Serum uric acid levels should be monitored and hypouricemic therapy instituted prior to the initiation of antileukemic therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Intravenous treatment of rats and mice, once every 21 days for 24 months, with NOVANTRONE resulted in an increased incidence of fibroma and external auditory canal tumors in rats

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FIRST PROOF

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19297/S021

MEDICAL REVIEW(S)

OCT 19 1999

Medical Officer Review: Changes Being Effected

NDA:	19-297 SLR 021	**Letter Date:**	October 8, 1999
Drug:	Novantrone (mitoxantrone)	**Review Date:**	October 19, 1999
Sponsor:	Immunex		

The sponsor submitted final labeling changes, previously agreed upon between DODP and the sponsor.

The sponsor agreed to delete the word[redacted] from the proposed labeling about interstitial pneumonitis.

The sponsor submitted sample labeling for the adverse event of extravasation: "Extravasation at the infusion site has been reported, which may result in erythema, swelling, pain, burning, and /or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Phlebitis has also been reported at the site of the infusion." We agreed that this wording was acceptable in June 1999.

Required regulatory action:

The project manager should prepare an action letter for the SLR.

Comments:

The proposed labeling is acceptable.

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/ MD 10-19-99

Grant Williams, M.D.
Team Leader

cc:
NDA 19-297/SLR 021
HFD-150/Division files
HFD-150/Susan Honig
HFD-150/Alvis Dunson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19297/S021

CHEMISTRY REVIEW(S)

NOV 1 1999

Chemistry Manufacturing Controls Review

NDA:	19-297/SLR-021 Amendment No. 001
Product:	NOVANTHRONE(mitoxanthrone) for Injection
Applicant:	Immunex Corporation
Date of Submission:	October 8, 1999
Stamp Data:	Oct .12, 1999
Date Assigned:	Oct. 26, 1999
Date of Review:	October 29, 1999
Material Reviewed:	NDA 19297/S-021 (SLR) Amendment 001
Other Documents:	

Labeling

The Description, Dosage and Administration, Preparation and Administration, Preparation for Intravenous Administration, and How Supplied sections submitted in this supplemental application were not revised from the approved one.

Conclusions and Recommendations.

No new CMC information is submitted in this supplement. Reference for CMC would have to be from previous approved application/ supplements. From a CMC view point, this supplement is approved.

/S/

Josephine M. Jee

Review Chemist, HFD-150, DNDC1

cc: NDA 19-297/S-021
HFD-150/Division File
HFD-150/JJee
HFD-150/RWood RHW 11-1-99
HFD-150/ADunson
F/T by JJee/ 10-29-99
R/D by:
File: 19297slr021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19297/S021

ADMINISTRATIVE DOCUMENTS

JAN 19 2000

Division of Oncology Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number(s): 19-297/S-021

Name of Drug: Novantrone (mitoxantrone for injection concentrate)

Sponsor: Immunex Corporation

Material Reviewed

1. NDA 19-297/S-021 dated May 21, 1999, received May 24, 1999
2. Sponsor fax dated June 14, 1999
3. Amendment #001 dated October 8, 1999, received October 12, 1999

Background and Summary Description:

The May 21, 1999 submission revises the **ADVERSE REACTIONS** section, **General/Pulmonary** subsection, and was submitted as Changes Being Effected (CBE). The medical officer recommended changes to the proposed labeling in a review dated June 1, 1999, and the sponsor submitted revised wording in a fax dated June 14, 1999. The medical officer in a review dated June 18, 1999,agreed the revised wording was acceptable.

The sponsor submitted an amendment to S-021 on October 8, 1999, and this was reviewed and agreed acceptable by the medical officer in a review dated October 19, 1999.

Review

Proposed changes to S-021 amendment #001

1. **ADVERSE REACTIONS** section, **General/Pulmonary** subsection:

   The following statement was revised as follows by the sponsor:

   "Interstitial pneumonitis has been reported in cancer patients receiving combination chemotherapy that included NOVANTRONE."

   Comment: This change was reviewed by the Medical Officer in the review dated October 19, 1999, for S-021 and was acceptable.

2. **ADVERSE REACTIONS** section, **General/Cutaneous**

The following statement was revised as follows by the sponsor:

"Extravasation at the infusion suite has been reported, which may result in erythema, swelling, pain, burning, and/or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Plebitis has also been reported at the site of the infusion."

Comment: This change was reviewed by the Medical Officer in the review dated October 19, 1999, for S-021 and was acceptable.

Recommended Regulatory Action:

I compared the packet insert for S-021, amendment 001, dated October 8, 1999, with the package insert for S-019 approved May 8, 1998, and recommend approval. Your acceptance of these changes is indicated by your concurrence below and supportive reviews.

/S/ 1/19/00
Alvis Dunson
Project Manager

concurrence: /S/ 1-19-00
Dotti Pease
Chief Project Manager

concurrence: /S/ 2/2/00
Susan Honig, M.D.
Medical Officer

concurrence: /S/ 2/2/00
Grant Williams, M.D.
Medical Team Leader

cc: Original NDA 19-297
HFD-150/Div. File
HFD-150/SHonig/GWilliams
HFD-150/ADunson/DPease

CSO REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19297/S021

CORRESPONDENCE

DUPLICATE

immunex

October 8, 1999

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NDA SUPP AMEND
SLR-021
(HF)

NOVANTRONE, mitoxantrone for injection concentrate
NDA 19-297/S-021, Amendment No. 001
Changes Being Effected –Labeling Supplement

Dear Dr. Justice:

Please refer to NDA 19-297 and to S-021. The original labeling supplement contained Immunex Corporation's revised package insert for Novantrone. The proposed package insert was revised to include a new adverse reaction to the **Adverse Reactions, General** section of the insert. The proposed text for the new adverse reaction statement was informally submitted to the FDA by facsimile on October 22, 1998 and the following text agreed upon:

"**Pulmonary:** Interstitial pneumonitis has been reported in cancer patients receiving combination chemotherapy that included NOVANTRONE."

In a facsimile dated June 4, 1999, the Medical Reviewer provided several comments on the FPL submitted with S-021. Specifically, it was requested that we delete the word from the statement above and that we add text to expand the cutaneous adverse events section of the label and provide some specific recommendations about extravasation. In a facsimile dated June 14, 1999, Immunex agreed to delete the term from the proposed language for interstitial pneumonitis and proposed the following regarding extravasation:

"Extravasation at the infusion site has been reported, which may result in erythema, swelling, pain, burning, and/or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Phlebitis has also been reported at the site of infusion."

NAS 11/5/99

DUPLICATE

51 University Street, Seattle, Washington 98101-2936
206.587.0430, Fax 206.587.0606 www.immunex.com

immunex

The Project Manager, Mr. Alvis Dunson, provided the proposed language to the Medical Reviewer for an informal review and communicated by telephone that the extravasation statement was acceptable as written.

Twelve copies of specimen labeling (package insert) are provided in which the above changes have been incorporated. The specimen labeling is identical in all respects to the PI that is packaged with product except it is not on typical package insert paper stock.

Twelve copies of Specimen Labeling incorporating the above changes is provided [1 copy for the medical reviewer (in one binder) and 11 copies for archival purposes. Upon approval of this supplement or within 30 days of implementation Immunex will provide 18 copies of the actual Final Printed Labeling.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 389-4066.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Manager, Regulatory Affairs

cc: Nancy Kercher
File 31100, 31543