CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-120

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

ACTION PACKAGE CHECKLIST

NDA # 21-120 Drug: Novantrone Injection DATE: December , 1999

Applicant: Immunex Corporation CSO: CDR Teresa Wheelous /Phone: 594-5504

User Fee Goal Date: December 4, 1999

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP____ AE✓ NA____ Yes_____ No_____
2. Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes✓ No_____
3. Completed copy of this CHECKLIST in package TYPE 6 NDA	Chem/Ther Types Appr. Product N19-297
4. LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft✓ Revised Draft_____ Final_____
5. PATENT INFORMATION	✓
6. EXCLUSIVITY CHECKLIST	
7. PEDIATRIC PAGE	
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	✓
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo expaining why.	
10. REVIEWS:	
DIVISION DIRECTOR'S MEMO (If more than 1 review for any 1 discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented)	✓
GROUP LEADER'S MEMO	N/A
MEDICAL REVIEW	✓
SAFETY UPDATE REVIEW	✓
STATISTICAL REVIEW	✓
BIOPHARMACEUTICS REVIEW	✓
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	✓
Statistical Review of Carcinogenicity Study(ies)	✓
CAC Report/Minutes	
CHEMISTRY REVIEW	N/A
Labeling and Nomenclature Committee Review Memorandum	N/A
Date EER completed _____ (attach signed form or CIRTS printout) FUR needed _____ FUR requested _____	OK_____ No_____
Have the methods been validated?	Yes (attach)_____ No_____
Environmental Assessment Review / FONSI	Review_____ FONSI_____
MICROBIOLOGY REVIEW	
What is the status of the monograph?	
11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	
12. MINUTES OF MEETINGS Date of End-of-Phase 2 Meeting Nov 2, 1998 Date of pre-NDA Meeting April 12, 1999	
13. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes_____ Info Alert_____ Transcript✓ No mtg_____ Jan. 28, 2000
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	
15. If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes_____ No_____ Yes, documentation attached_____ No, included in AP ltr _____
16. INTEGRATED SUMMARY OF EFFECTIVENESS	
17. INTEGRATED SUMMARY OF SAFETY	

revision: 3/7/96

XI. PATENT INFORMATION & CERTIFICATION (Items 13 & 14)

PATENT CERTIFICATION

(1) NDA Number: 21-120

(2) Applicant: Immunex Corporation, Seattle, Washington 98101

(3) Drug: NOVANTRONE® (mitoxantrone hydrochloride)

(4) Indication: Indicated for the treatment of secondary progressive multiple sclerosis.

(5) Strength: 20 mg, 25 mg or 30 mg per vial

(6) Dosage Form: Parenteral

(7) Certification:

Pursuant to Section 505(j)(2)(A)(vii) of the "Drug Price Competition and Patent Term Restoration Act of 1984", Applicant herein makes the following certification based on his opinion and to the best of his knowledge and belief:

(i) U.S. Patent No. 4,278,689, expiring July 14, 2000, claims pharmaceutical compositions in dosage unit form comprising the listed drug.

(ii) U.S. Patent No. 4,820,738, expiring April 11, 2006, covering a method of using the drug to treat leukemia and solid tumors.

APPEARS THIS WAY
ON ORIGINAL

(8) Effective Date of Approval:

Applicant requests that approval be made effective immediately since U.S. Patents No. 4,278,689 and 4,820,738 are assigned to Immunex Corporation.

Respectfully submitted,

_____
Michael K. Kirschner
Managing Counsel, Intellectual Property
Registration No. 34,851
Attorney for Applicant

COUNTY OF KING)
) SS.
STATE OF WASHINGTON)

Sworn to and subscribed before me this _____ day of _____, 1999.

_____
Notary Public

APPEARS THIS WAY
ON ORIGINAL

DEBARMENT CERTIFICATION

Immunex Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 (a) or (b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Nancy L Kercher

Nancy L. Kercher
Director, Regulatory Affairs
Immunex Corporation

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: October 1, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-120

SUBJECT: Response to Approvable letter of 3/1/00 for NDA 21-120, for the use of Novantrone (mitoxantrone) in patients with various forms of Multiple Sclerosis (MS)

On 3/1/00, the Division sent an Approvable letter to Immunex Corporation for NDA 21-120, for the use of mitoxantrone in patients with various forms of progressive/worsening MS. In that letter, the Division asked the sponsor to 1) respond to several questions raised at the 1/28/00 meeting of the Peripheral and Central Nervous Systems Advisory Committee, 2) submit additional metabolism data, 3) submit revised labeling, including a Medication Guide, and 4) create a registry of all patients treated with Novantrone, in order to insure that all patients would be appropriately monitored for cardiac toxicity. In addition, the letter described a Phase 4 commitment for the submission of additional pharmacokinetic data.

The sponsor responded to the letter first in a submission dated 4/13/00, and subsequently provided further clarifications/plans in submissions dated 5/22/00, 7/28/00, 8/10/00, and 8/28/00.

These submissions have been reviewed by Dr. Boehm (reviews dated 8/3/00, 8/9/00, and 8/31/00) and Dr. Racoosin (memos dated 8/3/00 and 9/1/00) of the Division's safety group, Dr. Fetterly of the Office of Clinical Pharmacology and Biopharmaceutics (review dated 8/7/00), and Karen Lechter, of the Division of Drug Marketing, Advertising, and Communications (review dated 8/22/00).

In this memo, I will briefly review the sponsor's responses to the clinical questions posed in the Approvable letter, and give the basis for the Division's action.

Clinical Questions

1) In the Approvable letter, we asked the sponsor to document that the relapses seen in the trials were rated as "severe". This was important because, since the diagnoses of relapses were made by unblinded observers in both Studies 901 and 902, the Committee felt that unblinding would be a considerably less critical problem if the relapses were "severe'.

Study 901

In this study, the sponsor noted that there were 2 criteria for the diagnosis of a severe relapse:

a) a new symptom with a change in Kurtzke functional score of greater than or equal to 2 for more than 2 days, or
b) deterioration of an existing symptom of at least 1 point in the pyramidal, brainstem, cerebellar, and/or visual system for more than 2 days.

The sponsor notes that there were 17 severe relapses in the mitoxantrone 12 mg/m^2 group, compared to 60 in the placebo group. In both groups, the percentage of severe relapses which were associated with a change in Kurtzke of at least 2 points (relapses that either met criterion a above or had a deterioration of at least 2 points in one system or of 1 point in at least 2 symptoms) was about 70%. A comparison between the treatment groups of the proportion of relapses that met the criterion of at least a 2 point deterioration as defined in the previous sentence yielded a p-value of 0.004.

Study 902

While functional scores were not specifically recorded at the time of relapse in this study, the unblinded rater did categorize the relapses into one of three categories:

1) Discrete-Functional status worsens by no more than 1 point on the scale for each functional system
2) Moderate-Worsening of 2 points in a functional system, or 1 point in at least 2 functional systems
3) Severe-Worsening of greater than 2 points in at least one functional system or more than one point in each of at least 2 functional systems

The categories Moderate and Severe as defined here are equivalent to the definition of Severe used in Study 901. A total of 26/38 (68%) of relapses in this study were rated as Moderate or Severe (3/7-43%-in the mitoxantrone group and 23/31-74%-in the control group). A comparison between groups of the number of relapses meeting this definition was significant (p=0.001) in favor of mitoxantrone.

2) The sponsor was asked to document that patients in both studies had experienced progression of their neurologic disability prior to study entry.

Study 901

In this study, patients had deteriorated on average about 1.5-1.6 points on the EDSS in the 18 months prior to study entry. Most of the patients (about 85-88%

in each group) deteriorated between 1-2 points during this period (indeed, most of these deteriorated 1 point).

Study 902

According to the sponsor, the disability scores were not prospectively collected distant in time prior to study entry in this study. However, the sponsor performed a retrospective scoring on the EDSS based on patients' medical records in a window of between 8 and 16 months prior to their entry into the study (this retrospective assignment was performed by both [redacted] one of the investigators, and independently by a 3 person panel of company employees). This analysis demonstrated that patients had deteriorated on average about 2.2 points on the EDSS (most patients had deteriorated between 1-2.5 points).

3) We asked the sponsor to document that EDSS scores were not systematically obtained during exacerbations. Further, we asked the sponsor to document that the effect on EDSS seen in Study 901 was robust (i.e., that it persisted for at least 3-6 months). This was important because the EDSS was rated by an unblinded rater in Study 902.

Study 901

The sponsor documented that only 8/124 (6.5%) of the EDSS measures used in the primary analyses of Study 901 were performed within 56 days of a relapse, and none were done within 13 days of a relapse. In addition, only 75/858 (8.7%) of all evaluations in this study were performed within 56 days of a relapse.

Study 902

Because assessments were performed every 4 weeks in this study, the chance that EDSS scores could be affected by relapses was greater than in Study 901. The sponsor performed 2 analyses to address this concern.

First, the sponsor excluded patients who experienced a relapse in the month prior the Month 0 or Month 6 evaluation (this was intended to minimize a bias in favor of drug from an artificially high EDSS in the mitoxantrone group at Month 0 and in the control group at Month 6). This analysis yielded a p-value of 0.008 in favor of the mitoxantrone group.

In addition, the sponsor had reported in the original application that there were significant differences favoring the drug group in the number of patients who had deteriorated by at least one point on the EDSS (from Month 0 to Month 6) as well as in the number of patients who had improved by at least 1 point over this period. In the re-submissions, these same comparisons were made including only those patients who experienced these same degree of changes at Month 4 that persisted during Months 5 and 6. In this analysis, the nominal p-value in

favor of drug for the proportion of Deteriorations was 0.08, while for the proportion of Improvers it was <0.001.

Biopharmaceutics Questions

The sponsor submitted in vitro data to address the inhibitory effect of [redacted] mitoxantrone on CYP 450 enzyme systems. These studies demonstrated that mitoxantrone did not inhibit 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Induction of CYP 1A2 and 3A4 was observed at 100 mcM of mitoxantrone.

An evaluation of the enzymes involved in mitoxantrone metabolism was undertaken in human liver microsomes. Surprisingly, at 0.1 and 1 mcM concentrations of mitoxantrone, the amount of parent drug present at the end of incubation was greater than that prior to incubation for all CYP 450 enzymes tested. At 10 mcM, the amount pre- and post-incubation was about the same. Dr. Fetterly speculated that one possible explanation for these findings was related to the sensitivity of the assay for mitoxantrone, although at the moment these results must be considered unexplained.

Additional in vitro assays suggested that mitoxantrone induced CYP 450 2E1, and that only parent and a glucuronide metabolite were present after 20 hours of incubation with human hepatocytes.

APPEARS THIS WAY
ON ORIGINAL

Post-Marketing Issues

While the Division had requested in the Approvable letter that the sponsor create a registry that would include all patients treated with mitoxantrone, we subsequently agreed that two complimentary studies would be sufficient to adequately assess the safety of the treatment in patients with progressive MS.

First, the sponsor will conduct a "mini-registry" in which 500 patients in the first year [redacted] will be closely monitored according to labeled requirements (in particular, cardiac function to be assessed at baseline, whenever there are symptoms of cardiac toxicity, and prior to each visit once the cumulative dose reaches 100 mg/m^2). The results of these tests will be collected centrally and will provide rapid evaluation of the safety of the treatment. This experience should be able to provide an accurate assessment of the incidence of serious outcomes; if no events of concern are seen, this experience will provide a cap on the maximum risk of a serious outcome of about 0.6% (incidentally, in Dr. Boehm's and Racoosin's last memos, they discuss the sponsor's apparent lack

of monitoring absolute neutrophil nadir and duration of neutropenia; these deficiencies have been corrected).

Second, the sponsor will undertake a surveillance program to assess physician compliance with the labeled monitoring regimen. Details of this proposal have not yet been submitted.

In addition, the sponsor is developing plans to disseminate educational information to physicians and patients, to alert them to the potential risks of treatment with mitoxantrone. [redacted]

Labeling

We have reached agreement with the sponsor on the labeling. It is worth noting that, while the Approvable letter requested that the sponsor draft a Medication Guide, we have agreed that the information to be given to the patient will be in the form of a Patient Package Insert, or PPI (as I understand it, a fundamental difference between the two is that it is a requirement that a Medication Guide be given to the patient, whereas there is no such formal requirement that the PPI be given to the patient). We decided that the PPI would be acceptable because given the nature of the treatment (it is always given by a health care practitioner, and not taken by the patient at home), we were confident that it would be given to the patient. Specifically, it is anticipated that the physician will give the PPI to the patient at an office visit prior, and in close temporal proximity, to each treatment. The effectiveness of this system will also be assessed by the sponsor's surveillance program.

Pharmacokinetics

As described in the Approvable letter, there are a number of PK issues that will need to be addressed in Phase 4. The sponsor has agreed to complete these studies by the end of 2001.

COMMENTS

I have concluded that the sponsor has adequately responded to the clinical questions posed in the Approvable letter. They have also adequately responded

IMMUNEX

September 7, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

APPEARS THIS WAY
ON ORIGINAL

RE: **NDA 21-120, Amendment No. 018**
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Revised Protocol and CRF

Dear Madam or Sir:

Enclosed please find three copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. Please refer to your facsimile of September 5, 2000 that provided comments from the safety review team on the protocol and CRF for the post-marketing "registry" study to be conducted with Novantrone. We have incorporated the recommended changes in the documents and the amended protocol and CRF are attached. Copies of them were also provided by facsimile on September 7, 2000. The specific changes involved deletion of the phrase "who are not receiving oral contraceptives" from the protocol such that all women of child bearing potential will be required to have a pregnancy test prior to each dose of Novantrone. Also, page 7 of the CRF has been modified to allow for collection of ANC nadir and duration of neutropenia.

If you have any questions or comments regarding this submission, please contact me at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

cc: Dawn Viveash
File

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

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA #	NDA 21-120
DATE:	06-SEP-00
PRODUCT NAME:	Novantrone® for Injection
COMPANY NAME:	Immunex Corporation
SUBJECT:	Samples of Labeling Materials
CONVERSATION WITH:	Mark Gauthier, Senior Manager, Regulatory Affairs
TELEPHONE #:	(206) 381-6266

I contacted Mark Gauthier by telephone, 3:48 PM EDT, 9/05/00. I requested samples of the packaging materials for Novantrone (cartons and vial labels). He said that he could have them sent to me by Federal Express the following day. We confirmed that the correct destination would be the document room for HFD-120. I also made the recommendation that the labeling for Novantrone use the USAN (2) name for the drug substance. I pointed out the difference in the names, which is in the name of the parent ring. The USAN (1) name identifies it as 9,10-anthracenedione and the USAN (2) name identifies it as anthraquinone. Mr. Gauthier accepted the recommendation and said that it could be easily incorporated with the other labeling changes that were being made with the packaging insert.

The packaging specimens arrived the following day, 06 September 2000.

/S/

Thomas A. Broadbent, Ph.D.
Review Chemist

APPEARS THIS WAY
ON ORIGINAL

cc: HFD-120/NDA 21-120
HFD-120/DivFile
HFD-120/MGuzewska
HFD-120/TBroadbent
HFD-120/TWheelous

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA #	NDA 21-120
DATE:	05-SEP-00
PRODUCT NAME:	Novantrone® for Injection
COMPANY NAME:	Immunex Corporation
SUBJECT:	Samples of Labeling Materials
CONVERSATION WITH:	Mark Gauthier, Senior Manager, Regulatory Affairs
TELEPHONE #:	(206) 381-6266

I contacted Mark Gauthier by telephone, 3:48 PM EDT, 9/05/00. I requested samples of the packaging materials for Novantrone (cartons and vial labels). He said that he could have them sent to me by Federal Express the following day. We confirmed that the correct destination would be the document room for HFD-120. I also made the recommendation that the labeling for Novantrone use the USAN (2) name for the drug substance. I pointed out the difference in the names, which is in the name of the parent ring. The USAN (1) name identifies it as 9,10-anthracenedione and the USAN (2) name identifies it as anthraquinone. Mr. Gauthier accepted the recommendation and said that it could be easily incorporated with the other labeling changes that were being made with the packaging insert.

/S/

Thomas A. Broadbent, Ph.D.
Review Chemist

APPEARS THIS WAY
ON ORIGINAL

cc: HFD-120/NDA 21-120
HFD-120/DivFile
HFD-120/MGuzewsk.
HFD-120/TBroadbent
HFD-120/TWheelous

/S/

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859
Telecopier Cover Sheet

NOTE: THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone at (301) 594-2850 and return it to us at the above address by mail.

DATE:	**September 5, 2000**
TIME:	**11:35 AM**
DELIVER TO:	Mark Gauthier
Fax Number:	(206) 223-0468
Phone Number:	(206) 381-6266

APPEARS THIS WAY ON ORIGINAL

FROM:	**Teresa Wheelous**
	301-594-2850
	Project Manager

Total number of pages, including cover page: 1

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:
Mark,
These are comments from the safety review team regarding August 10, 2000 request for information submission for Novantrone's post-marketing study.

1. On page 7 of the CRF, in the "Infection Table", two additional pieces of information need to be recorded: ANC nadir and duration of neutropenia. Spaces for this information could potentially be included in the column "Associated with severe neutropenia"
2. You have amended the protocol to include pregnancy tests prior to each dose for those women of childbearing potential who are not receiving birth control pills. Since oral contraceptives do not protect against pregnancy 100% of the time, pregnancy testing prior to Novantrone therapy should not be conditioned on the type of contraceptive being used. All women should received pregnancy tests prior to each Novantrone dose.

DESK COPY

IMMUNEX

August 29, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

RE: NDA 21-120, Amendment No. 017
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Draft Labeling – Patient Package Insert

Dear Madam or Sir:

Enclosed please find three copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. Please refer to our April 13, 2000 submission (Response to Approvable Letter, Amendment No. 10) in which we provided a draft Medication Guide for use with the product. Based on recent input, we have reformatted the Medication Guide as a Patient Package Insert. The title has been changed to PPI, the black box warning has been inserted, followed by the text that had been sent previously as a Medication Guide. We would appreciate receiving any comments from the reviewing Division and DDMAC at the earliest convenience.

If you have any questions or comments regarding this submission, please contact me at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Dawn Viveash
File

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Immunex Corporation	August 29, 2000
TELEPHONE NO. *(Include Area Code)* (206) 587-0430	FACSIMILE (FAX) Number *(Include Area Code)* (206) 223-0468
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 51 University Street Seattle, WA 98101 USA	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Immunex Corporation 51 University Street Seattle, WA 98101

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mitoxantrone hydrocloride	NOVANTRONE
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)* Intravaneous
DOSAGE FORM: Injection	STRENGTHS: 20mg,25mg,30mg(2mg/ml)
ROUTE OF ADMINISTRATION:	

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 19-297, :

WITHHOLD 6 PAGE (S)

draft labeling

(A)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages
+ 3 pages

7 pages

DESK COPY

immunex

August 28, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 21-120, Amendment No. 015
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Response to Request for Information

Dear Ms. Wheelous:

Enclosed please find one desk copy of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. Please refer also Amendment No. 10 dated April 13, 2000 and to Amendment No. 014 dated July 25, 2000 and to your facsimile dated August 7, 2000 that provided comments from the safety reviewer regarding Protocol 31.0007, the "registry" study we plan to initiate as soon as possible after approval of the NDA. In the August 7 facsimile, the safety reviewer requested several changes be made to the protocol for the prospective study to be conducted to monitor safety of the product when used according to the package insert. We have incorporated most of the changes or provided rationale for not incorporating them. Our responses to items 1 – 7 are provided in Attachment 1. In addition, in item 8 the reviewer asked that we provide the current status of the programs discussed during the March 28, 2000 teleconference, specifically an "Assessment of Novantrone Dosing and Monitoring in MS in a Range of Practice Settings" and an "Educational Plan and Marketing Research Assessment". The Educational Plan materials have been developed as outlined in previous submissions and can be finalized as soon as labeling discussion have been completed. In order to move forward with the retrospective study in a range of practice settings, a synopsis has been written and a CRO identified to conduct the study. The study will be initiated as soon as the drug is approved and there is sufficient experience in general practice to allow an evaluation of the data. This too is addressed in Attachment 1. The FDA comments are shown in bolded text in the attachment followed by Immunex Corporation's response to each.

The following attachments are provided:

1. Responses to Items 1 – 8 of the August 7 facsimile
2. Amendment No. 1 to Protocol 31.0007

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

IMUNEX

3. Revised Case Report Form for Protocol 31.0007
4. A copy of the synopsis of the "Assessment of Novantrone Dosing and Monitoring in MS in a Range of Practice Settings" (previously provided in Amendment No. 10 dated April 13, 2000)
5. A copy of the "Educational Plan and Marketing Research Assessment" (previously provided in Amendment No. 10 dated April 13, 2000)
6. Draft Medication Guide

If you need additional copies of this amendment or have any questions or comments regarding this submission, please contact me at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Dawn Viveash
File

APPEARS THIS WAY
ON ORIGINAL

IMMUNEX

Immunex Corporation
Regulatory Affairs
51 University Street
Seattle, WA 98101

Phone: 206 381-6266
Fax: 206 223-0468

FAX MESSAGE - PLEASE DELIVER IMMEDIATELY

Send to: Merril Mille — Fax: (301) 594-2858

From: Mark W. Gauthier — Date: August 22, 2000

Total Number of Pages: 37 INCLUDING THIS PAGE

COMMENTS:

RE: NDA 21-120, Novantrone

Mr. Mille,

As we discussed by phone this morning, I am forwarding a copy of a new revision to the package insert for Novantrone. Please provide copies to the review team to substitute this version for the one provided by facsimile on August 21. We have deleted the new language in the Clinical Pharmacology and related sections first presented in the July 21, 2000 package insert and reverted back to the previously approved wording. The Biopharm review cannot be completed until we submit the outstanding final reports for the remaining 2 of the 4 required in vitro metabolism studies. Early in the process, we obtained agreement from Dr. Katz that the results of the in vitro metabolism studies could be submitted post-approval, and labeling revised accordingly, if all other issues had been addressed. Dr. Katz also pointed out during our August 18 teleconference that he was deferring comments on the Clinical Pharmacology section until all pending issues there were resolved. #3

We now feel that we have adequately addressed and incorporated all of the Agency's concerns and comments related to the package insert and should be very close to approval. The one outstanding issue that still requires resolution is the patient package insert. In our April 13, 2000 response to the approvable letter we included a Medication Guide. Late in April an electronic version was sent by e-mail to Teresa Wheelous to forward to DDMAC for review and determination of whether it would be in the form of a Medication Guide or a PPI. Based on our conversation of this morning it now appears that it could be 2 more weeks before DDMAC comments on format and content of the document are available. Would it be possible to obtain a response from the DDMAC reviewer by Monday August 28? This would allow us to finalize the PPI and resubmit it the next day and not significantly delay approval, if that is the only outstanding issue.

I would appreciate any feedback you can provide.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Manager, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

Immunex Corporation

DUPLICATE

immunex

CENTER FOR DRUG EVALUATION AND RESEARCH

- AUG 22 2000

RECEIVED HFD-120

August 21, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

ORIG AMENDMENT
N-(BL)

RE: NDA 21-120, Amendment No. 016
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Draft Labeling

Dear Madam or Sir:

Enclosed please find three copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. Please refer to your facsimile dated August 16, 2000 (revised package insert) and to the teleconference that took place on August 18, 2000. We have incorporated all of your recommended changes noted in the August 16th letter with the exception of the specific items we discussed during the August 18 teleconference. Highlights of what we agreed upon during the August 18th phone call are listed on the attached pages. Several typographical errors and some inadvertent omissions noted in the latest FDA version have been corrected. Please refer to Attachment 1 for a summary of the agreements reached during the August 18th teleconference. A revised version of the package insert incorporating all of these agreed upon changes is provided in Attachment 2.

Three sections of the package insert have been revised to reflect text previously approved (refer to NDA 19-297/S-021) by the Division of Oncology Drug Products. In S-021 to NDA 19-297, the Oncology Division approved the wording for the ADVERSE REACTIONS, GENERAL, Cutaneous section pertaining to extravasation at the injection site. We feel that the stronger language previously approved by Oncology should remain in the PI. Similarly, in the DOSAGE AND ADMINISTRATION, Preparation and Administration Precautions section, that is a similar statement regarding extravasation, again, we feel the previously approved wording should remain. The last related change is also in the ADVERSE REACTIONS, GENERAL, Pulmonary section regarding interstitial pneumonitis. When this change was approved under NDA 19-297/S-021, the Oncology Division objected to the use of the term [redacted], therefore, we have deleted this term from the draft package insert.

51 University Street, Seattle, Washington 98101-2936
206 587 0430 Fax 206 587 0606 www.immunex.com

IMMUNEX

If you have any questions or comments regarding this submission, please contact me at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Dawn Viveash
File

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER:

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Immunex Corporation	August 21, 2000
TELEPHONE NO. *(Include Area Code)* (206) 587-0430	**FACSIMILE (FAX) Number** *(Include Area Code)* (206) 223-0468
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 51 University Street Seattle, WA 98101 USA	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Immunex Corporation 51 University Street Seattle, WA 98101

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mitoxantrone hydrocloride	NOVANTRONE

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)* Intravaneous

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	20mg,25mg,30mg(2mg/ml)	

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 19-297,

Number of Pages Redacted 72

❖❖❖

Draft Labeling
(not releasable,

(F)

Summary of August 18, 2000 teleconference

1. **Secondary endpoints**
We discussed the possible inclusion of the data from the secondary endpoints from Study 1. Dr. Katz explained Divisional policy regarding use of secondary endpoints in the label.

2. **Second paragraph of indication statement**
Immunex provided alternative language by facsimile prior to the teleconference. Dr. Katz did not object but recommended that we modify it to specify that these were the criteria used in the trial not necessarily a definition of one stage of the disease.

Outcome: the second paragraph will now read:

"The clinical patterns of multiple sclerosis in the studies were characterized as follows: secondary progressive and progressive-relapsing disease were characterized by gradual increasing disability with or without superimposed clinical relapses, and worsening relapsing-remitting disease was characterized by clinical relapses resulting in a step-wise worsening of disability."

Pregnancy
Immunex explained that certain practices have already been established regarding the safe use of Novantrone in the oncology setting, therefore we would appreciate being able to differentiate between MS patients and oncology patients regarding certain testing. Dr. Katz understood our concerns and we agreed to modify the FDA language slightly to allow for this.

Outcome: the statement that FDA had put in the insert will be modified slightly as follows:

3. **Black Box**

For reasons similar to those described above, Immunex requested to be allowed to differentiate between MS and oncology in regard to the black box warning on monitoring for cardiotoxicity. Dr. Katz agreed that this would be acceptable and would confirm with the Oncology Division that our revised statement was satisfactory.

Outcome: the black box will now include the qualifying statement as before and the 2 affected sentences will read as follows:

Electronic Mail Message

Date: 8/18/00 9:45:48 AM
From: GauthierM (GauthierM@immunex.com)
To: wheeloust (wheeloust@A1)
Subject: NDA 21-120

Teresa,

Upon further review of the package insert you provided recently, we felt that the wording changes made to the second paragraph of the indication statement for MS were a bit confusing. Would you please share the following revised paragraph with Dr. Katz prior to the telecon this morning?

Revised text:

I apologize for not providing this sooner. I know it is going to come up in our discussions later this morning and I thought it may facilitate the discussion if you had a written version to react to rather than verbal only during the call.

Thanks,

Mark

APPEARS THIS WAY
ON ORIGINAL

immunex

Immunex Corporation
Regulatory Affairs
51 University Street
Seattle, WA 98101

Phone: 206 381-6266
Fax: 206 223-0468

FAX MESSAGE - PLEASE DELIVER IMMEDIATELY

Send to:Teresa Wheelous Fax: (301) 594-2858

From: Mark W. Gauthier Date: August 16, 2000

Total Number of Pages: 2 INCLUDING THIS PAGE

COMMENTS:

RE: NDA 21-120, Novantrone

Teresa,

We would like to discuss several issues in a teleconference to include Dr. Katz and other members of the review team related to the most recent FDA version of the package insert. In one instance, we are providing language that we would prefer be included in the PI that is valid, relevant to clinical practice, and provides valuable information for the practicing neurologist who treats MS patients. Specifically, we propose inclusion of the following two paragraphs in the Clinical Trials section:

Three other items that we want to discuss are:

1. Obtain clarification on the rationale for rewording the second paragraph of the indication statement for MS,
2. The impact of requiring a pregnancy test prior to each dose of Novantrone in the oncology setting, and
3. Clarification of certain changes to the black box warning.

APPEARS THIS WAY ON ORIGINAL

If at all possible, we would like to schedule the teleconference on Thursday or Friday, August 17 or 18, to resolve these issues. I will contact you by phone on Thursday morning to schedule.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 28

❖❖❖

Draft Labeling
(not releasable,

C

Immunex Corporation

DESK COPY

immunex

August 10, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 21-120, Amendment No. 015
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Response to Request for Information

Dear Madam or Sir:

Enclosed please find three copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. Please refer also Amendment No. 10 dated April 13, 2000 and to Amendment No. 014 dated July 25, 2000 and to your facsimile dated August 7, 2000 that provided comments from the safety reviewer regarding Protocol 31.0007, the "registry" study we plan to initiate as soon as possible after approval of the NDA. In the August 7 facsimile, the safety reviewer requested several changes be made to the protocol for the prospective study to be conducted to monitor safety of the product when used according to the package insert. We have incorporated most of the changes or provided rationale for not incorporating them. Our responses to items 1 – 7 are provided in Attachment 1. In addition, in item 8 the reviewer asked that we provide the current status of the programs discussed during the March 28, 2000 teleconference, specifically an "Assessment of Novantrone Dosing and Monitoring in MS in a Range of Practice Settings" and an "Educational Plan and Marketing Research Assessment". The Educational Plan materials have been developed as outlined in previous submissions and can be finalized as soon as labeling discussion have been completed. In order to move forward with the retrospective study in a range of practice settings, a synopsis has been written and a CRO identified to conduct the study. The study will be initiated as soon as the drug is approved and there is sufficient experience in general practice to allow an evaluation of the data. This too is addressed in Attachment 1. The FDA comments are shown in bolded text in the attachment followed by Immunex Corporation's response to each.

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

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The following attachments are provided:

1. Responses to Items 1 – 8 of the August 7 facsimile
2. Amendment No. 1 to Protocol 31.0007
3. Revised Case Report Form for Protocol 31.0007
4. A copy of the synopsis of the "Assessment of Novantrone Dosing and Monitoring in MS in a Range of Practice Settings" (previously provided in Amendment No. 10 dated April 13, 2000)
5. A copy of the "Educational Plan and Marketing Research Assessment" (previously provided in Amendment No. 10 dated April 13, 2000)
6. Draft Medication Guide

If you have any questions or comments regarding this submission, please contact me at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Dawn Viveash
File

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Immunex Corporation	August 10, 2000
TELEPHONE NO. *(Include Area Code)* (206) 587-0430	**FACSIMILE (FAX) Number** *(Include Area Code)* (206) 223-0468
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 51 University Street Seattle, WA 98101 USA	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Immunex Corporation 51 University Street Seattle, WA 98101

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mitoxantrone hydrocloride	Novantrone
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	**CODE NAME** *(If any)* Intravenous

DOSAGE FORM.	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	20mg,25mg,30mg(2mg/ml)	

(PROPOSED) INDICATION(S) FOR USE: Treatment of secondary - progressive multiple sclerosis

APPLICATION INFORMATION

APPLICATION TYPE (check one): ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

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Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one): ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one): ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 19-297,

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
✔	19. OTHER (Specify) Response to request for information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Mark W. Gauthier	Mark Gauthier, Sr. Mgr., Regulatory Affairs	8/10/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Immunex Corporation 51 University St. Seattle, WA 98101	(206) 381-6266

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

6 pgs

IMMUNEX

July 25, 2000

N-(BM)

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

RE: NDA 21-120, Amendment No. 014
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Draft Labeling
New Protocol – No. 031.0007, "Registry"
Case Report Form – Protocol 031.0007

Dear Madam or Sir:

Enclosed please find three copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. Please refer to the draft labeling included with the March 1, 2000 approvable letter for NDA 21-120, to the draft labeling included in Amendment 011 to NDA 21-120 dated May 22, 2000, and to the June 8, 2000 telephone contact with Ms. Teresa Wheelous (request from Safety Reviewer).

In the approvable letter and the draft package insert provided by FDA, there were several sections that required revision based on the outcome of the in vitro metabolism studies. The draft package insert included in this submission has been revised to reflect the results of those studies. The updated language for each of the sections affected is provided on a cover sheet immediately preceding the revised package insert. A copy of the latest version of the package insert is being submitted simultaneously to NDA 19-297 to facilitate the joint review with the Division of Oncology Drug Products.

In the June 8 telephone contact with Ms. Wheelous, she relayed that the safety reviewer would like to review the final protocol for the prospective study (registry) and the sample case report forms (CRFs), when available. A draft protocol for the study was provided in the April 13 submission to the NDA. The protocol has now been finalized and is provided in this submission. It is based upon the proposed indication statement, dose, and regimen as described in Amendment No. 011. Although the safety reviewer informally stated that the proposed Novantrone registry design included in the April 13 submission incorporates the information the Division requested during previous teleconferences, it may be necessary to revise the protocol if there are changes in the proposed indication. We have included a copy of the final draft of the CRF to be used to collect safety and efficacy data from the prospective study as well.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Immunex Corporation	July 25, 2000
TELEPHONE NO. *(Include Area Code)* (206) 587-0430	**FACSIMILE (FAX) Number** *(Include Area Code)* (206) 223-0468
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 51 University Street Seattle, WA 98101 USA	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Immunex Corporation 51 University Street Seattle, WA 98101

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mitoxantrone hydrochloride	Novantrone

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	20mg,25mg,30mg(2mg/ml)	Intraveneous

(PROPOSED) INDICATION(S) FOR USE: Treatment of secondary - progressive multiple sclerosis

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 19-297,

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APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 39

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Draft Labeling
(not releasable,

(K)

Immunex Corporation

immunex

May 22, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

RE: NDA 21-120, Amendment No. 011
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Response to Request for Additional Information

Dear Madam or Sir:

Enclosed please find nine copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. This submission is provided in response to requests from FDA conveyed during the May 4, 2000 teleconference regarding the complete response to the approvable letter of March 1, 2000 (refer to Amendment 010 to NDA 21-120 dated April 13, 2000). During the teleconference, Dr. Katz requested that Immunex provide the following:

1. Study 902 - Methodology used to collect and analyze the data on functional scores for determination of relapse severity.

2. Study 901 and 902 - Methodology used to evaluate the occurrence and potential impact of recent relapses on the EDSS values used for the primary analysis.

3. A correction was made on page 011 of Amendment No. 10 to the NDA (response to approvable letter) dated April 13, 2000. In addition, revisions have been made to the data to reflect new analyses. The data presented in the April 13 response defined a month as 30 days. The revised analysis standardizes the time intervals to 14-day increments. This change resulted in minor adjustments to the counts in the early time periods. The original calculation included all EDSS evaluations, including baseline, as a denominator. By protocol definition, patients were excluded if they had experienced a relapse within the 8 weeks preceeding study entry. Therefore, exclusion of baseline evaluations from the denominator is a more conservative approach.

4. The sponsor should provide data from original NDA referenced in the submission dated April 13, 2000.

51 University Street, Seattle, Washington 98101-2936
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5. The response should be provided in an integrated manner, indicating any data deficiencies and providing supporting data or arguments that help to substantiate our claims.

The submission is formatted to facilitate ease of review and, as described below, represents a fully integrated response to the clinical questions in that the newly requested information has been incorporated into the response provided in the April 13 resubmission.

The response is formatted as follows:

An integrated response to each of the three clinical questions from the March 1 approvable letter is provided. The response to each question is formatted as follows: we have reiterated the previous (April 13) response to the question, followed immediately by the additional clarifications requested in the May 4 teleconference. Appendices included in the April 13 response retain the same designation (Appendices A-E) and are included in Attachment 1 of this document. All attachments are provided after the integrated responses to the clinical questions (April 13 responses and newly added information). Our April 13th response referenced material from the original NDA. This material has been included in this response and is indicated by bolded text in the responses.

This submission addresses all aspects of the clinical questions raised in the approvable letter and includes additional clarification as requested in the May 4 teleconference. It clearly presents the way in which the data were collected and analyzed; presents the methodology used to evaluate occurrence and impact of relapses on EDSS assessments; provides robust data to support approval of this NDA for the indication requested; and supports the conclusions that we have made based upon the dataset and/or trial design.

With the completion of this step, we feel that it is now appropriate to bring several other items requiring resolution to your attention:

1. **Finalization of labeling:** We would like to schedule a teleconference within the next 2-3 weeks to reach agreement with you on the text of the package insert. I will contact the Project Manager approximately one week after receipt of this submission to discuss a mutually agreeable date to have this discussion.

2. **Finalization of protocols:** Protocols for the prospective registry and the retrospective chart review were provided in our April 13 response. We have discussed protocol design on two previous occasions (March 28 and April 13,

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2000) and feel we have agreement on the major elements. We have identified a CRO to conduct the studies and have a meeting scheduled with potential

NARCOMS investigators on June 22, 2000 at the annual meeting of the CMSC (Consortium of MS Centers). It would be most helpful to hear any comments you have by June 12, 2000. Our goal is to be in a position to initiate the studies immediately upon approval. Dr. Donald Goodkin is joining Immunex as an employee and will oversee the registry and other aspects of the MS program.

3. It is critical that the education plan (including information on safety and monitoring) described in the April 13 response be in place at the time of approval. To implement the plan, we need to finalize the labeling to allow time for submission to and review of our promotional materials by DDMAC for pre-clearance.

4. Preliminary data from the first two in vitro metabolism studies will be submitted to the NDA before the end of the week.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 381-6266.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File

APPEARS THIS WAY
ON ORIGINAL

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
✔	19. OTHER (Specify) Response to request for information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Mark W. Gauthier	Mark Gauthier, Sr. Mgr., Regulatory Affairs	May 19, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Immunex Corporation 51 University St. Seattle, WA 98101	(206) 381-6266

Wheelous

NDA 21-120

MAY 15 2000

Immunex Corporation
Attention: Mark Gauthier, Sr. Mgr., Regulatory Affairs
51 University Street
Seattle, WA 98101

Dear Mr. Gauthier:

We acknowledge receipt on April 17, 2000 of your April 13, 2000resubmission to your new drug application for Novantrone (mitoxantrone) for injection.

This resubmission contains additional analyses of clinical data, a post approval safety monitoring program (Registry), and a commitment to provide final study reports of the *in vitro* metabolism studies by July 1, 2000 as agreed upon during the March 28,2000 telecon.

We consider this a complete, class 2 response to our March 1, 2000 action letter.

Therefore, the user fee goal date is October 17, 2000.

With the submission of the final study reports and this amendment, we have received a complete response to our March 1, 2000 action letter.

If you have any question, call Ms. Teresa Wheelous, Regulatory Project Manager, at (301) 594-2850.

Sincerely yours,

/S/

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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April 13, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

RE: NDA 21-120, Amendment No. 010
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
General Correspondence – Complete Response to Approvable Letter

Dear Madam or Sir:

Enclosed please find five copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. This submission addresses all of the FDA comments raised in the approvable letter dated March 1, 2000, with the exception of the in vitro metabolism data. As agreed during the March 28, 2000 teleconference between Immunex and DNDP, we hereby commit to provide draft reports for each of the in vitro studies as they become available and to submit final reports by July 1, 2000

During the March 28 teleconference, noteworthy agreements were reached that impact on the content and timing of the Immunex response to the approvable letter. Submission of the in vitro metabolism data, as stated above, will be allowed separately from the rest of the responses. The initial submission of the response without the metabolism data will not be considered "incomplete" by the Agency. In addition, if the Division completes their review and determines the NDA can be approved prior to July 1, 2000, it was agreed that the in vitro metabolism data can be submitted post-approval.

The post-approval safety-monitoring program ("Registry") was also resolved during the March 28 teleconference. Concurrence was attained on the following components of a multifaceted approach to ensure patient safety and compliance with the package insert:

1. Immunex will conduct a 500 patient, prospective, open-label safety monitoring study of Novantrone post-approval. Patients will be dosed and monitored in accordance with the package insert.

2. Immunex will conduct a periodic patient record review, c
, to assess compliance with recommendations on cumulative

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dose limits and patient monitoring. This study will assess the effectiveness of the education program and determine how well physicians translate this information regarding Novantrone dosing and monitoring into their practice. Data to be submitted annually.

3. Immunex will undertake a comprehensive educational program to ensure and reinforce compliance with approved labeling. Additional efforts (over and above Item #2) will be made to evaluate physician awareness and compliance with safety and monitoring guidelines.

In Attachment 1, each of the FDA comments are listed individually followed by Immunex Corporation's response. When necessary, additional documents are appended to the responses. A copy of the approvable letter is provided in Attachment 2. Attachment 3 includes a copy of the minutes of the March 23, 2000 teleconference with OCPB; minutes of the March 28 teleconference with DNDP are provided in Attachment 4.

As agreed to in the teleconference of April 13, 2000, Immunex will provide updates on the key safety information to the Division as follows. Upon approval, periodic reports will be submitted in the usual format on a quarterly basis for the first 3 years. Normally, this would revert to annually 3 years after approval. We, like the Agency, feel that there may be a need for more frequent reports, therefore, beginning 3 years after approval of the NDA, safety updates for the prospective study will be submitted every 6 months.

In addition, Immunex will provide serious reaction reports of cardiotoxicity and myelosuppression to the division within 15 calendar days. We recognize that some of these events would not meet the standard criteria for expedited reporting since they will be considered "expected" per the package insert.

Per our discussion of April 13, 2000, Immunex will submit detailed descriptions of the methodology that will be utilized for both of the studies prior to approval of the NDA and implementation of either study.

Immunex Corporation would like to reinforce that we, like the Agency, are very committed to implementing programs to ensure compliance and patient safety while making this important drug available to a patient population with no currently approved therapeutic options. We feel that the mutually agreed upon approach will satisfy both FDA's and our desire to ensure patient safety, but more importantly, will best serve the MS community.

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If you have any comments or questions regarding the contents of this submission, please contact me at (206) 381-6266.

Sincerely,

on behalf of
Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File

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Number of Pages Redacted 38

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Draft Labeling
(not releasable,

Number of Pages Redacted 5

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Draft Labeling
(not releasable,

APR - 5 2000

Medical Reviewer: Comments on revised labeling

NDA:	19-297 SLR-022	**Letter Date:**	March 30, 2000 (via fax)
Drug:	Novantrone	**Review Date:**	April 4, 2000
Sponsor:	Immunex		

The sponsor submitted an sNDA to the Division of Neuropharmacological Drug Products for Novantrone for the treatment of multiple sclerosis. In accordance with regulations, the labeling supplement for this indication was submitted to the Division of Oncology Drug Products. The DODP waited until DNDP completed its review and reached an approval decision before reviewing the labeling supplement. Comments were conveyed to the sponsor. The facsimile sent 3/30/00 contains revised text for the black box warning in the package insert. The sponsor hopes for comments prior to drafting a response to the Approvable Letter from DNDP.

Reviewer Comments:

1. You should use the epirubicin label as a general guide, as epirubicin is the most recently approved anthracycline agent.

2. The first 4 statements [redacted] are acceptable.

3. The section on cardiotoxicity should be revised. The epirubicin label, for example, states

[redacted]

- The first statement listed above should begin the mitoxantrone black box warning on cardiotoxicity, substituting the relevant drug name.
- Your second statement [redacted] is acceptable if " [redacted] " is deleted. New agents are available for cancer treatment, and it is unknown whether cardiotoxicity is increased when mitoxantrone is given with these new drugs.

- Your third statement should be amplified, using the last two sentences quoted from the epirubicin label as a template.

4. The leukemia warning is not acceptable. It should be modified to:

"Secondary acute myelogenous leukemia (AML) has been reported in cancer patients treated with anthracyclines. NOVANTRONE is an anthracenedione, a related drug. The occurrence of refractory secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Secondary leukemias have been reported in cancer patients treated with NOVANTRONE in combination with other cytotoxic agents; the incidence of these events has not been quantified."

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/ 4/5/00

Grant Williams, M.D.
Team Leader

cc:
NDA 19-297/SLR 022
HFD-150/Division files
HFD-150/Susan Honig
HFD-150/Alvis Dunson
HFD-120/T. Wheelous

APPEARS THIS WAY
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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

April 1, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 21-120, Amendment No. 009
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
General Correspondence

Dear Madam or Sir:

Enclosed please find five copies of an amendment to Immunex Corporation's NDA #21-120 submitted on June 4, 1999. As discussed during the teleconference on March 28, 2000, we are providing copies of several items in draft form for your review and comment prior to finalization.

Immunex Corporation would like to reinforce that we, like the Agency, are very committed to successfully and effectively implementing the programs described in Items 1, 2 and 3, to ensure compliance and patient safety. These 3 programs (No.'s 1-3) are complex and will require significant planning and lead-time. Therefore, we are most interested in obtaining the Agency's concurrence on the concepts now to allow us to move forward with implementation while review of our response is in progress. We feel that this approach will satisfy both FDA's and our desire to ensure patient safety, but more importantly, will best serve the MS community.

Therefore we would appreciate receiving your comments by Thursday morning April 6 so we can incorporate them into our response to the approvable letter that we intend to submit on April 10. Each of the items is listed below with brief comments.

1. Proposal for a Prospective, Open-Label Safety Monitoring Study of Novantrone in a Selected Cohort of MS Patients – This document provides additional details of the study we proposed previously (February 9, 2000 facsimile). The study will enroll a minimum of 500 patients; the sample size agreed during our March 28 teleconference. Data will be collected prospectively, periodically summarized and reported to the Agency.

   Please confirm that the study as outlined is acceptable.