CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-120

APPROVAL LETTER

NDA 21-120

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

Dear Mr. Gauthier:

Please refer to your new drug application (NDA) dated June 2, 1999, received June 4, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novantrone (mitoxantrone hydrochloride) Injection.

We acknowledge receipt of your submissions dated:

May 22, 2000	May 24, 2000	July 12, 2000	July 25, 2000
August 10, 2000	August 21, 2000	August 29, 2000	September 5, 2000

Your submission of April 13, 2000 constituted a complete response to our March 1, 2000 action letter.

This new drug application provides for the use of Novantrone (mitoxantrone hydrochloride) Injection for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). NOVANTRONE is not indicated in the treatment of patients with primary progressive multiple sclerosis.

We have completed the review of this 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 agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on

heavyweight paper or similar material. Alternatively, you may submit the FPL

electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-120." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632)(21 CFR 314.55 (or 601.27)).

Reference is made to your correspondence dated September 29, 1999, requesting a waiver for pediatric studies.

We have reviewed the information you have submitted and agree that a waiver is justified for Novantrone for secondary progressive and progressive relapsing multiple sclerosis for the pediatric population. Accordingly, a waiver for pediatric studies for these two populations is granted under 21 CFR 314.55 at this time.

However, the agency has not made a determination if a health benefit would be gained by studying Novantrone in pediatric patients with worsening relapsing-remitting multiple sclerosis. FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations. Please submit a rationale for waiving pediatric studies in this population by January 12, 2001. FDA will reply whether pediatric studies are required under the rule. If FDA determines at that time that pediatric studies are necessary, FDA will also set a specified time at which you must submit the required assessments.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA. To comply with these regulations, all 3-day and 15-day alert reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 19-297 for this drug product, not to this NDA. This includes the quarterly periodic adverse drug experience reports required by this new NDA. In the future, any submission specific to multiple sclerosis should be forwarded to this division only as a courtesy desk copy. No submissions should be made to this NDA except for the 20 copies of the final printed labeling as requested above.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration

5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

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

PHASE 4 COMMITMENTS:
Biopharmaceutics

1. PK requests were conveyed to you in the November 4, 1998 End of Phase II meeting, the April 12, 1999 Pre-NDA meeting, and in comments from the original review of NDA 19-297 (March 5, 1986) as well as in comments from a supplemental review of NDA 19-297 (November 13, 1996) prior to the submission of this NDA and during the review of the approved Novantrone NDA. In addition, these deficiencies were communicated to you in the Approvable letter of March 1, 2000. Specifically, the deficiencies are:

    A. The application is lacking a validated analytical method for the determination of mitoxantrone concentration in biological fluids and tissues.
    B. Adequate information about the metabolic fate and pathway of mitoxantrone has not been provided.
    C. There is inadequate evaluation of the kinetics of mitoxantrone, including a determination of the terminal half-life, as well as a lack of an analysis of the kinetics by gender, age, and race.
    D. Drug – drug interactions have not been provided.

2. No information about the kinetics of mitoxantrone is available for patients with multiple sclerosis.

The due date for completion of these commitments is December 31, 2001.

Safety

- Please provide the results of the "Prospective, Open-Label Safety Monitoring Study of Novantrone in a Selected Cohort of Multiple Sclerosis Patients" in the time frame previously agreed upon.
- Please provide a detailed plan of your proposed "Assessment of Novantrone Dosing and Monitoring in MS in a Range of Practice Settings" and its results as they become available.

- Please provide the results of your Marketing Research Assessment of your proposed Education Plan (Appendix C of your April 1, 2000 submission).

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

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

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-120

APPROVABLE LETTER

NDA 21-120

MAR - 1 2000

Immunex Corporation
Attention: Mark W. Gauthier
Senior Regulatory Affairs Manager
51 University Street
Seattle, WA 98101

APPEARS THIS WAY
ON ORIGINAL

Dear Mr. Gauthier:

Please refer to your new drug application (NDA) dated June 2, 1999 received June 4, 1999, submitted under section 505(b) the Federal Food, Drug, and Cosmetic Act for Novantrone (mitoxantrone hydrochloride) Injection 20 mg, 25 mg, 30 mg (2 mg/ml).

We acknowledge receipt of your submissions dated:

August 13, 1999	September 10, 1999	September 27, 1999
September 29, 1999	October 1, 1999	October 14, 1999
October 15, 1999	October 26, 1999	November 5, 1999

In addition, we refer to a meeting of the Peripheral and Central Nervous Systems Advisory Committee meeting of January 28, 2000, in which this application was discussed. At that meeting, as you know, the Committee concluded that substantial evidence of effectiveness and sufficient evidence of safety had been submitted to support approval of the application.

We have completed the review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

Clinical

1 As you know, the Advisory Committee concluded that Novantrone had demonstrated an effect on decreasing the relapse rate in both Studies 901 and 902. However, given that relapses were diagnosed by unblinded observers in both studies, the Committee was able to conclude that the drug had an effect on relapses only because of your assertion that the relapses were, in general, rated as "severe", and therefore their diagnosis was not likely to have been affected by blind breaking. In order for us to conclude definitively that the treatment does have an effect on relapses, you must submit evidence that, in fact, these relapses were severe. In particular, it

would be useful to document how many of the relapses met each specific criteria of "severe" that were described at the Advisory Committee meeting.

2 In addition, the Committee concluded that the treatment has an effect on "worsening" relapsing-remitting patients based on your assertion that patients in Study 902 did, indeed, progress on their EDSS prior to enrollment. Please submit the data that support this conclusion.

In addition, patients enrolled in Study 901 were said to have progressive disease as well (either chronic progressive or relapsing progressive). Please submit evidence, analogous to that requested above for Study 902, that documents that patients in Study 901 were, indeed, progressive.

3 It is critical to establish that the EDSS scores in both studies were not obtained during, or closely temporally related to, exacerbations. Were this to be the case, they would be unreliable indicators of a patient's chronic neurologic status. Please submit documentation that, in general, EDSS scores were obtained removed in time from relapses.

In addition, because EDSS scores in patients in Study 902 were also rated by an unblinded rater, there is no valid independent replication of the effect on progression of neurologic status that was ostensibly shown in Study 901. For this reason, in order for a claim for an effect on neurologic status (as measured by EDSS) to be considered, we must be assured that the effect seen in Study 901 was a robust finding. Toward this end, it is important that you document that the effect seen on EDSS in Study 901 was persistent and not transient; i.e., the effect, once achieved, persisted for a reasonable duration (e.g., 3-6 months). We would be happy to explore with you ways to examine this question.

Biopharmaceutics

As we have discussed with you on several occasions, the metabolism of Novantrone is not well characterized. For this reason, and given the introduction of this treatment into the MS population, a population significantly different than the ones for whom Novantrone is currently indicated, it is critical that you obtain additional information about Novantrone's metabolism prior to its approval for the MS population. This information may be obtained from in vitro assays; our staff of the Office of Clinical Pharmacology and Biopharmaceutics will be happy to discuss with you the specific studies needed.

Labeling

We have included draft labeling with this letter. In some places we have drafted specific language which differs from that you proposed; we ask that you adopt this language verbatim. In other places, we have inserted notes to you that will require you to draft additional language. It is important to note that this labeling should be considered provisional at this time; in addition to changes that you may propose, it may need to undergo extensive revision depending upon the results of our analyses of the data we have requested above.

In addition, we believe that labeling should include information to be given to the patient. Please draft such a document in the form of a Medication Guide (see 21 CFR 208.20 for the content and form of a Medication Guide). The document should focus on the specific symptoms patients should be aware of that are related to the major toxicities seen with Novantrone (e.g., cardiotoxicity, hematologic), and should also emphasize the fact that cardiac monitoring must be performed after a cumulative dose of 100 mg/m^2, and that ordinarily a dose of 140 mg/m^2 should not be exceeded. Whether this information will ultimately be contained in such a guide, or in a patient package insert, remains to be determined. In addition, it will be necessary to have further discussions to agree on a mechanism that will insure that patients receive this information, given that the treatment is not dispensed directly to the patient to be self-administered.

Registry

As you know, we believe that the safe use of Novantrone in MS patients requires that they be evaluated for cardiac toxicity at and beyond a cumulative dose of 100 mg/m^2. We continue to believe that the most reliable way to assure that all patients are appropriately monitored is for all patients to be enrolled in a registry, so that their cumulative dose can be centrally recorded. Such a system has the advantage of being capable of not only assuring that the treating physician is aware of the time at which monitoring becomes mandatory, but also can, ideally, detect when a patient has reached the maximum dose, thereby preventing inappropriate overdosage. We will be happy to discuss this issue with you.

In addition to the information needed to be submitted and reviewed prior to approval, we ask you to agree to address the following deficiencies as a Phase 4 commitment:

PHASE 4 COMMITMENTS:

Biopharmaceutics

I PK requests were conveyed to you in the November 4, 1998 End of Phase II meeting, the April 12, 1999 Pre-NDA meeting, and in comments from the original review of NDA 19-297 (March 5, 1986) as well as in comments from a supplemental review of NDA 19-297 (November 13, 1996) prior to the submission of this NDA and during the review of the approved Novantrone NDA. Several of these deficiencies are still outstanding. Specifically, the deficiencies are:

A The application is lacking a validated analytical method for the determination of mitoxantrone concentration in biological fluids and tissues.

B Adequate information about the metabolic fate and pathway of mitoxantrone has not been provided.

C There is inadequate evaluation of the kinetics of mitoxantrone, including a determination of the terminal half-life, as well as a lack of an analysis of the kinetics by gender, age, and race.

D Drug – drug interactions have not been provided.

II No information about the kinetics of mitoxantrone is available for patients with multiple sclerosis.

In future submissions please provide adequate summaries of the individual PK reports and literature to facilitate Agency review.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.
2. Retabulation of dropouts with new dropouts identified. Discuss, if appropriate.
3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Ms. Teresa Wheelous, R.Ph., Regulatory Project Manager, at (301) 594-2850.

Sincerely Yours,

/S/ 1/1/00

APPEARS THIS WAY
ON ORIGINAL

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

Number of Pages Redacted 22

❖❖❖

Draft Labeling
(not releasable,

m