MEMORANDUM

DATE: January 2, 2000

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

TO: Members, Peripheral and Central Nervous Systems Drugs Advisory Commitee

SUBJECT: January 28, 2000 Advisory Committee Meeting to Discuss NDA 21-120, for the use of Novantrone to Treat Patients with Multiple Sclerosis

As you know, the PCNS Advisory Committee will be meeting on 1/28/00 to discuss NDA 21-120, submitted on 6/2/99 by Immunex Corporation, for the use of Novantrone (mitoxantrone) in patients with Multiple Sclerosis (MS). The sponsor's proposed Indication is "To slow progression of neurologic disability and reduce the relapse rate in patients with progressive multiple sclerosis". Novantrone is an anthracenedione that causes DNA strand breaks, interferes with RNA, and is a potent inhibitor of topoisomerase II. In the United States, it is approved for use in adults with Acute Non-Lymphocytic Leukemia, and for the treatment of pain in patients with symptomatic hormone refractory prostate cancer. It is approved in 50 countries as a treatment for various other cancers.

In this application, the sponsor has submitted the results of 2 randomized controlled trials which the sponsor believes establish the effectiveness of Novantrone as a treatment for patients with progressive MS. In addition, the application contains safety data for over 500 unique individuals with MS treated with at least one dose of Novantrone, as well as literature reports of safety experience in patients with various cancers.

In this package, we have included the review of the safety data, performed by Dr. Boehm of the Division (review dated 11/5/99), the statistical review of the effectiveness data, performed by Dr. Yan of the Division of Biometrics (review dated 11/26/99), the currently approved Novantrone package insert, and this memo. In this memo, I will briefly review the effectiveness and safety data, and outline the issues we would like the Committee to discuss at the 1/28/00 meeting. The sponsor has prepared its own briefing document, which is being sent to you under separate cover.

EFFECTIVENESS

Study 031.0901

This was a randomized, placebo controlled, rater blinded, parallel group multi-center trial comparing the effects of 12 mg/m^2, 5 mg/m^2, and placebo in patients with secondary progressive or remittent-progressive MS in an active phase of disease. Eligible patients

were to receive treatment with study drug as an intravenous infusion every 3 months for 8 cycles, for a total study duration of 24 months. Patients were required to have an EDSS score of between 3 (able to walk unassisted) and 6 (needs assistance to walk). The EDSS is a standard scale used to assess function in patients with MS, and ranges from 0 (Normal neurological exam) to 10 (Death related to MS), with half-steps.

In this trial, the patients and treating neurologists were unblinded to treatment assignment, but an assessing neurologist at each center was blinded to treatment assignment.

The primary outcome in this study was a multi-variate test which combined results from the following 5 measures comparing the high dose to placebo:

1) Mean Change from Baseline in EDSS at 24 Months
2) Mean Change from Baseline in Ambulation Index (a commonly used 10 point scale ranging from 0-Normal to 9-Wheelchair, which measures increasing difficulty with ambulation)
3) Number of Relapses requiring steroid treatment
4) Time to First Relapse requiring steroid treatment
5) Mean Change from Baseline in Standardized Neurologic Status (a newly created scale which measures 5 functional groups: Definite Supraspinal Signs, Paresis, Spasticity, Sensation, and Bladder Impairment; each group has multiple sub-functions, each of which is given a numerical rating, the rating scale differing for each subfunction)

If the overall test was significant, each primary variable was to be tested in the following order: EDSS, AI, number of attacks, time to first attack, and SNS. Statistical testing was to be performed on an individual measure only if the preceding measure achieved statistical significance at p=0.05.

A number of secondary measures, all functions of the various primary measures, were also assessed. In addition, those patients enrolled at centers that had the capability, were assessed by gadolinium enhanced MRI and T2 weighted MRI.

Results

A total of 194 patients were enrolled at 17 centers in Germany, Belgium, Hungary, and Poland. The following chart (taken from the sponsor's Table 10.1.B, page 6 of Dr. Yan's review) displays the disposition of patients in the study:

	Placebo	Nov 5 mg/m2	Nov 12 mg/m2
Randomized	65	66	63
Completed	47 (72%)	54 (82%)	48 (76%)
Included in ITT Analysis	64 (98%)	64 (97%)	60 (95%)

For patients who did not complete the trial, the median time in study was 342 days for the placebo patients, 501 days for the low dose, and 385 days for the high dose group.

Half of the ITT population (N=94) were diagnosed with secondary progressive MS; half (N=94) with progressive relapsing MS. Approximately 45% of the placebo and high dose groups were diagnosed with progressive relapsing MS, while about 58% of the low dose group carried that diagnosis.

Patients were comparable on demographic measures at baseline. On average, patients had had about 1.3 relapses in the 12 months prior to study entry, and deteriorated about 1.5-1.6 points on the EDSS over the 18 months prior to enrollment.

The following table displays the results for the individual outcome measures:

Test	Baseline			Change at 24 Months			P-value vs Pla	
	Pla	5 mg/m^2	12 mg/m^2	Pla	5 mg/m^2	12 mg/m^2	5 m/m^2	12 m/m^2
EDSS	4.69	4.64	4.45	0.23	-0.23	-0.13	0.0098	0.0194
AI	2.63	2.52	2.52	0.77	0.41	0.30	0.0560	0.0306
#Relapses Treated				76.8	46.9	24.1	0.0293	0.0002
Time to First Treated Relapse Median (Months)				14.2	NR	NR	0.0549	0.0004
SNS	20.94	18.88	19.33	0.77	-0.38	-1.07	0.2912	0.0269

The overall difference between the 12 mg/m2 group and the placebo group was 0.3094, a number that has no easily understood clinical meaning; the p-value for the overall test was 0.0001. As Dr. Yan notes, however (Page 17), neither the sponsor nor she have a detailed understanding of the software used to run this analysis.

MRI

As noted above, MRIs were performed at a subset of the centers in the trial. Results were read blinded independently by 2 experts who then reached a consensus on each scan. The following subset of patients received MRI scans at Baseline, 12 months, and 24 months:

	N
Placebo	36 (56%)
Nov 5 mg/m^2	40 (63%)
Nov 12 mg/m^2	34 (57%)

The following results were seen:

Measure	Placebo			N 5mg/m^2			N 12 mg/m^2		
	Base	M12	M24	Base	M12	M24	Base	M12	M24
# of Pts with Gd + lesions	8	7	5	19	6	4	10	5	1
# of Pts with new Gd+ lesions		7	5		6	4		4	0

Measure	Placebo			N 5mg/m^2			N 12 mg/m^2		
	Base	M12	M24	Base	M12	M24	Base	M12	M24
Mean # of Gd+ lesion	0.44	0.31	0.28	3.23	0.30	0.11	1.88	0.15	0.03
Mean Change From Base In # of Gd+ lesions		-0.14	-0.19		-2.93	-3.27		-1.74	-2.03
P-value for Mean Change From Baseline						0.0031			0.095

Study 031.0902

This was a multi-center, parallel group, open, parallel group controlled trial in patients designed to evaluate the effectiveness of Novantrone in patients with "severe" MS. In this study, patients with severe (defined as those patients who had a current risk of presenting a major handicap) and active (based on having had at least 2 attacks in the year prior to enrollment or progression characterized as an increase in Kurtzke score of at least 2 points after an attack- i.e., secondary progressive MS) disease were randomized to receive either Novantrone 20 mg plus methylprednisolone or methylprednisolone alone, given intravenously once a month for 6 months. Neither the patient nor the treating neurologist was blind to treatment assignment.

The primary outcome measure in this study was the percentage of change from baseline in the number of patients without active lesions on MRI at each month of the study. An active lesion was defined as a new lesion (not present at baseline), a lesion present at baseline that increased in size, or Gd enhancement. The protocol did not state (nor did the study report) if lesions that were Gd+ at baseline and were still Gd+ during treatment (but that did not increase in size) were to be considered active lesions.

All MRIs were read by a single blinded expert reviewer.

Eligible patients entered a 2 month pre-randomization period, during which they were scanned at Month –2, Month –1, and Month 0. The Month –1 and Month 0 scans were each taken 1 month after an intravenous dose of 1 gm of methylprednisolone. Patients who developed at least 1 new Gd+ lesion during this period of time were randomized after the Month 0 scan.

Results

A total of 42 patients (21 in each group) were randomized at 5 centers in France. A total of 5 patients withdrew after treatment initiation; all in the control group, all due to marked deterioration in disease.

Of the 21 Novantrone treated patients, 15 (71%) had relapsing-remitting MS, while 6 (29%) had secondary progressive MS. Of the control patients, 17 (81%) had relapsing-remitting MS, while 19% had secondary progressive disease.

Patients were comparable at baseline in demographic measures. On average, patients had had MS for about 6 years prior to enrollment, with an average of about 2-3 relapses in the year prior to enrollment.

The following chart, taken from sponsor's Table 6.1.1 (reprinted in Dr. Yan's review, page 26), displays the results, by month, of the primary measure, the number of patients without active lesions, as previously defined:

Month	Novantrone	Control	P-value
M-1	3/20 (15%)	3/20 (15%)	1.000
M0	2/20 (10%)	1/21 (5%)	0.606
M1	3/21 (14%)	4/21 (19%)	1.000
M2	11/21 (52%)	3/21 (14%)	0.009
M3	13/21 (62%)	6/21 (29%)	0.030
M4	13/21 (62%)	7/20 (35%)	0.085
M5	14/21 (67%)	5/16 (31%)	0.033
M6	19/21 (90%)	5/16 (31%)	0.001

The primary measure was the percent change in the number of patients without active lesions at Month 6 compared to Baseline (defined as Month-2). This was significant with p=0.011.

The following chart, taken from sponsor's Table 6.1.2.A (Dr. Yan's review, page 27) displays the results of the Mean Number of New Gd+ Lesions:

Month	Novantrone	Control	P-value
M-1	6.8	9.1	NS
M0	4.6	5.1	NS
M1	1.9	12.3	0.036
M2	2.6	5.7	0.017
M3	1.1	9.2	0.011
M4	-0.9	8.9	0.035
M5	0.6	3.8	0.009
M6	0.1	2.9	0.001

The sponsor also evaluated EDSS in this study; the following chart, taken from sponsor's Table 6.2.1.A (Dr. Yan's review, page 28) displays the results of the analyses of the Mean Change from Baseline (defined as Month 0) by month:

Month	Novantrone		Control		P-value
	Mean EDSS	Change	Mean EDSS	Change	
M0	4.5	---	4.6	----	
M1	4.2	-0.3	4.9	0.2	NS
M2	4.1	-0.4	4.9	0.3	0.024
M3	3.9	-0.6	5.0	0.3	0.008
M4	3.6	-0.9	5.1	0.6	0.001
M5	3.4	-1.1	4.5	0.1	0.002
M6	3.4	-1.1	4.3	-0.1	0.013

SAFETY

The NDA contains safety information from several datasources; because Novantrone has been approved in the US since 1987 for the treatment of Acute Non-Lymphocytic Leukemia, and since 1996 for the treatment of pain in patients with hormone resistant prostate cancer, Dr. Boehm has reviewed data from our Post-Marketing reports for certain selected adverse events, and the sponsor has provided some information from Novantrone's use in patients with various cancers. In addition, of course, the sponsor has submitted detailed safety data from the 2 controlled trials discussed above, as well as from a cohort of patients treated over a number of years in an MS clinic in Germany.

Because the dosing regimens and durations of treatment used in the 2 controlled trials are quite distinct, I will describe the safety experience from these 2 trials separately. In addition, because the German experience was open and uncontrolled, I will describe that separately as well.

Exposure

Experience in a total of 599 unique patients with MS receiving at least one dose of Novantrone is described in the NDA (Study 31.0901, N=124; Study 31.0902, N=21; German Study, N=454). While the data from the 2 controlled trials was documented in a prospective manner, the German experience represents all the patients treated in this clinic over a 10 year period (1988-1998), the data from which was extracted onto case report forms (CRFs) retrospectively. Patients in this latter cohort were not monitored in as formal a way as those in the controlled trials, and follow-up for these patients was less complete. Most patients in the German cohort were treated with 12 mg/m^2 every 3 months.

Study 31.0901

Exposure

A total of 122 patients received Novantrone for at least 6 months in this trial, and 111 received drug for 1 year. The mean cumulative dose was about 83 mg/m^2 in the high dose group and 37 mg/m^2 in the low dose group. The highest cumulative dose achieved in this study was 96 mg/m^2, which corresponds to the dose achieved if all doses in the high dose group were given.

Deaths

No deaths were reported during this trial. There were no deaths reported up to 12 months after the last dose, although complete follow-up was unavailable for 11 patients.

Discontinuations

A total of 17/64 placebo patients (27%) discontinued, compared to 10/64 low dose patients (16%) and 12/60 (20%) of high dose patients. A total of 2 (3%) of placebo and 5 (8%) of high dose patients discontinued due to adverse events. Of the 5 Novantrone patients discontinuing for adverse events, 1 had depression and suicidal ideation, 1 had left ventricular fractional shortening of 22% (baseline 41%, lower limit of normal 25%) after 4 doses which returned to 33% 1 year after discontinuation, 1 had persistent nausea and vomiting, one had a creatinine of 4.7 mg/dL associated with urinary retention and hydronephrosis which improved after catheterization of the bladder, and 1 had repeated UTIs.

Serious Adverse Events

The sponsor reported 10 serious AEs in each treated group (16% and 17% in low and high dose groups, respectively) and 6 (9%) in the placebo group.

In the high dose group, SAEs of interest not already discussed above included 2 cases of necrosis of the femoral head (both patients had previously received treatment with corticosteroids), hemorrhagic cystitis, which occurred after the first dose and did not recur with dose decrease, and endometritis.

Other Adverse Events

Over 85% of all patients in this trial reported at least one treatment emergent adverse event. The following table, taken from the sponsor's Table 12.1.2.A, reproduced in Dr. Boehm's review (page 13) lists those AEs that occurred in at least 5% of the high dose patients and for which the incidence was at least twice that of the placebo patients:

Event	Placebo (%)	Low Dose (%)	High Dose (%)
Nausea	20	55	76
Alopecia	31	38	61
UTI	13	29	32
Menstrual Disorder	26	51	61
Stomatitis	8	15	19
Amenorrhea	3	28	43
Leukopenia	0	9	19
Arrythmia	8	6	18
Gamma GT Increased	3	3	15
EKG abn'l	3	5	11
Sinusitis	2	3	6
Granulocyto-Penia	2	6	6
WBC abn'l	2	8	6
Anemia	2	9	6

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There was a dose response for cardiac adverse events, with 9% of placebo patients, 6% of low dose, and 21% of high dose patients reported as having had a cardiac adverse event; most of this difference was related to events coded as arrhythmia. In addition, about 3% of placebo patients, 5% of low dose patients, and 11% of high dose patients were

reported as having had an abnormal EKG. There was no further description of the nature of either the arrhythmias or abnormal EKGs reported.

Although about 86%, 77%, and 75% of patients randomized to low dose, high dose, and placebo, respectively, received all 8 courses of therapy, about 45% (N=27) of high dose and 9% (N=6) of low dose patients had their doses reduced secondary to adverse events. A total of 9 patients had their dose reduced because of hematologic toxicity (all in the high dose group), and 6 low dose and 22 high dose patients had their doses reduced secondary to non-hematologic toxicity; there are no further details about the nature of these toxicities.

Laboratory measurements were made at baseline and prior to each treatment course. Given this schedule of monitoring, it was impossible to characterize the true time course of any lab abnormalities.

Examination of the change from baseline in mean values for hematologic parameters revealed a dose related mean decrease in platelet count at 1 year and at study end, and examination of the proportion of outliers on these measures shows a dose related increase in the proportion of patients who met outlier criteria for platelet and WBC count as described below (taken from Dr. Boehm's table on page 16 of his review):

	Placebo	Low Dose	High Dose
WBC	7%	22%	37%
Platelets	5%	8%	11%

A total of 11 patients in the high dose, 4 patients in the low dose, and 2 patients in the placebo groups had neutrophil counts below $2x10^9/L$ at any time. No patient had a neutrophil count below $0.5x10^9/L$. Two patients (1 each in the low dose and placebo groups) had platelet counts below 100,000/cu mm.

Examination of the results of liver function testing revealed a very minor dose response in mean SGOT level, with a dose related increase in the proportion of patients who met outlier criteria for SGOT elevation as seen below (taken from Dr. Boehm's table, page 18 of his review):

	Placebo	Low Dose	High Dose
SGOT	15%	27%	30%

Further examination of these patients revealed no important differences across groups in the proportion of patients who had an SGOT>100U/L.

A total of 3%, 6%, and 8% of placebo, low dose, and high dose patients, respectively, had ejection fractions (assessed by echocardiography) at 24 months that were at least 10% lower than baseline levels. A total of 1(1.7%), 2(3.3%), and 3 (5.5%) of placebo, low

dose, and high dose patients, respectively, had ejection fractions of less than 50% of their baseline levels. There are no details provided about the patients' clinical status. As noted earlier, one subject (high dose) discontinued for a decrease in ejection fraction.

Although the sponsor did not provide complete follow-up at 36 months for all patients, 4 patients (3 low dose, 1 high dose) who had normal EFs at 24 months had further decreases at 36 months, as seen below (Dr. Boehm's table, page 19 of his review):

Patient	Dose	24 mth EF	36 mth EF
501	5	80%	53%
5302	5	61%	58%
5401	5	56%	45%
408	12	57%	40%

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Study 31.0902

Exposure

The mean cumulative dose in this study was about 81 mg/m^2, with a range of 62-101 mg/m^2 (recall that patients in this study received 20 mg once a month for 6 months).

Deaths

There were no deaths during this study.

Discontinuations

One patient in the Novantrone group was discontinued after the first dose due to elevated LFTs, which were attributed to fluoxetine. A total of 6 control patients discontinued treatment, all related to disease progression.

Serious Adverse Events

No SAEs were reported in this study.

Other Adverse Events

The following table, adapted from Sponsor's Table F.5.7., reproduced in Dr. Boehm's review, page 21, lists adverse events that occurred in greater than 5% (N>1) of Novantrone treated patients, and more than twice as frequently as in the control (methylprednisolone) group:

Event	Novantrone (%)	Control (%)
Amenorrhea	8 (53)	0
Alopecia	7 (33)	0
Nausea	6 (29)	0
Asthenia	5 (24)	0
UTI	4 (14)	1 (5)
Throat Infection	3 (14)	1 (5)
Gastralgia	2 (10)	0
Pharyngitis	2 (10)	0
Rhinitis	2 (10)	0
Mycosis	2 (10)	0
Aphthosis	2 (10)	0
Epigastric Pain	2 (10)	1 (5)

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Lab Testing

Hematology

Hematologic monitoring was performed every week for the Novantrone patients and every month for control patients.

Novantrone treated patients experienced slightly greater differences than controls in mean difference from Baseline at Month 6 in hemoglobin, WBC, neutrophils, and platelets. A total of 48% of Novantrone patients (10/21) had a WBC count below $2.0x10^9$/L, and none had a count below $1x10^9$/L at any time. A total of 19 Novantrone patients (90%) had a neutrophil count of less than or equal to $1x10^9$/L at least once during the trial, and 9 (43%) had at least one neutrophil count below $0.5x10^9$/L during the trial. All but 3 of these latter patients had neutrophil counts greater than $0.5x10^9$/L at the next measurement one week later. No subject (although there were some missing values) had neutrophil counts less than $0.5x10^9$/L by week 4 of any month of treatment.

Dr. Boehm has examined the risk of experiencing low neutrophil counts over time in the Novantrone treated patients (see his table, page 23 of his review). He has found that the risk of experiencing such events persists and/or increases over time. For example, displayed below are the risks for developing these abnormalities at Month 1 and Month 6:

Month	% with Count<$1x10^9$/L	% with Count<$0.5x10^9$/L
1	48%	10%
6	57%	29%

No Novantrone treated patients experienced a platelet count below 100,000/cu mm.

Other laboratory measurements were evaluated on a monthly basis. Novantrone treated patients had slightly greater mean increases (Month 6 compared to Month 0) in creatinine, AST, and alk phos compared to controls. There were no important differences between drug and control patients in the proportion of patients reaching outlier criteria for any lab measurement.

There was a slight increase in the number of Novantrone treated patients who met outlier criteria for decreased systolic and diastolic blood pressure and decreased hear rate at any time during the trial compared to the control treated patients, but the absolute systolic or diastolic pressures were not dangerously low.

Cardiac function was assessed at baseline and at Month 6 by EKG and echocardiogram. There were no important between treatment differences as measured by these assays.

German Cohort

As noted above, the sponsor identified a total of 454 patients treated at an academic referral center in Germany over the 10 year period 1988-1998. Data from the medical charts were transcribed onto a Case Report Form (CRF), but the sponsor did not have access to the original records. The occurrence of certain adverse events (e.g., cardiotoxicity, malignancies, treatment with antibiotics) was noted, but severity information was not collected. The following laboratory tests were recorded on the CRFs: leukocyte count, lymphocyte count, granulocyte counts, and immunoglobulin concentrations.

The standard dose in these patients was 12 mg/m^2 every 3 months. The mean number of doses received in this cohort was 4.4. A total of 85% of the patients received at least 2 doses, with 64% receiving at least 8 doses. The mean dose was 9.8 mg/m^2, and the mean cumulative dose was about 44 mg/m^2. A total of 93% of patients (424/454) received a cumulative dose of less than 100 mg/m^2, with the greatest cumulative dose being about 183 mg/m^2. The mean number of months of follow-up was about 47 months, with the longest duration of follow-up being about 121 months.

Deaths

There were a total of 20 deaths in this cohort. A total of 11 patients died greater than 3 years after their last dose and 3 died within 19 months of their last dose. A total of 8 deaths were attributed to pneumonia and 5 to insufficiency of breath, the cause of death was unknown for 3 patients, and the remaining 4 were attributed to bladder dysfunction/infections, cachexia, heart failure, and pulmonary infection + cardiomyopathia.

Discontinuations

According to the sponsor, 341 patients discontinued treatment; the other 113 were continuing to receive treatment at the time of the submission.

Of the 341 who discontinued, apparently 77 discontinued because they were treatment successes, and 44 discontinued because they were treatment failures. Dr. Boehm identified 32 patients who discontinued for adverse events (34 according to the sponsor), and 147 discontinued for Other reasons (not further specified, though most were listed as patient refusals), and the reasons were unknown for 4 patients and not completed for 15 other patients.

Of the 32 identified by Dr. Boehm as having discontinued for adverse events, 9 were for leukopenia, 5 were for lymphopenia, 5 were for cardiac events, 3 were for infection, 3 were for vomiting, and 1 each for weakness, reduced condition, increased liver enzymes, hepatitis C, very bad condition, skin necrosis, and no reason given. Dr. Boehm identified 7 patients whose reason for discontinuing treatment was given as "patient refusal" for whom the discontinuation appeared to have been associated with an adverse event (2 decreased leukocytes, 2 vomiting, 1 each alopecia, infection, decreased EF), and 4 whose reason for discontinuation was given as "treatment failure" in whom an adverse event appeared implicated (leukopenia, lymphopenia, infection, and alopecia).

No narrative descriptions of these events were included in the submission.

Serious Adverse Events

The sponsor asserts that there were no serious AEs reported.

Other Adverse Events

As noted above, information was collected about only a limited number of adverse events.

The sponsor reported that 38% of patients experienced an infection, 86% of which were called UTIs, and 12% of which were of unknown type. Few other additional details are available.

The sponsor reports that patients were examined with echocardiograms to assess clinical findings suggestive of cardiac toxicity and in those with a cumulative dose of at least 140 mg/m^2 before each treatment course. A total of 45% (203/454) had at least 1 echocardiogram and only 6 of these had a cumulative dose of at least 140 mg/m^2; therefore, as noted by Dr. Boehm, most of these patients were monitored for reasons that are not clear. Of the 203 patients in whom an echocardiogram was performed, 43 (21%) had an abnormality. These included ventricular dilation/dysfunction, pericardial effusion, and valvular abnormalities. Severity of these events was not recorded.

EKGs were routinely performed before each treatment course, and all but 1 patient had at least 1 EKG; the mean number/patient was 4.3. A total of 32% (143/453) had at least one abnormality, the most common being conduction block in 17% of patients. A total of 2% had ventricular hypertrophy.

According to the sponsor, 7 patients developed cardiac toxicity. The cumulative dose in these patients ranged from about 41 to 130 mg/m^2. Details were presented only for those patients who died. One was a 42 year old man treated with a cumulative dose of 91 mg/m^2 at the clinic between 1990-92. He then received an additional 120 mg between 1994-96 from his doctor. Two months after the last dose, he died in cardiogenic shock.

The second case was a 41 year old man who received a cumulative dose of 50 mg/m^2 at which time an echo showed diffuse hypokinesia of the left ventricle with a reduction of EF at rest. The drug was stopped, and the patient died during the next year (?date), with the death attributed to respiratory insufficiency during a URI.

A total of 12% of women reported amenorrhea, with 27% of these women recovering after therapy was discontinued. Information about the duration of treatment in the women who did not recover was not submitted in the application.

Lab tests

Hematology assessments were made prior to each treatment course. A total of 28 patients (6%) had WBC less than 2000/ cu mm, but none had a WBC below 1000/cu mm. A total of 62 patients (14%) had neutrophil counts between 500 and 1000/cu mm, with 12 patients having a neutrophil count below 500/cu mm. No additional data about these patients was submitted.

Post-Marketing Reports

Dr. Boehm has concentrated his examination on a subset of the 598 spontaneous reports of adverse events submitted to the Agency's database. This subset consists of reports of rhabdomyolosis, renal or hepatic failure, and congestive heart failure.

There were 2 reports of elevated CPK, both of which occurred in the context of an MI. There was a single report of a 46 year old woman with rhabdomyolosis and renal failure after a single course of Novantrone and cyclophosphamide.

There were 5 reports of liver failure, 4 of which occurred in the context of multi-organ failure. The remaining case was a 15 year old female treated with Ara-C and Novantrone for AML. She developed slightly elevated ALT and AST 2 weeks after the first treatment course, after which she received a second (reduced) dose after the enzymes had normalized. About a month later, she was jaundiced (bilirubin 2.6 mg%) and had LFTs between 3-4000U/L. She died with massive hepatic necrosis observed on autopsy.

A total of 15 reports of renal failure occur in the Agency's post-marketing database, none of which seemed to be a primary event. A number of the cases occurred in patients receiving other nephrotoxic drugs, in the setting of multi-organ failure, or the cases were inadequately described.

Cardiac Toxicity

There was a single case reported of cardiac toxicity in an MS patient. This was a 32 year old woman (treated in Belgium) who developed massive, refractory cardiac failure 2 months after her last dose of Novantrone. She had received a cumulative dose of about 170-180 mg/m^2 over an unknown duration. She had been receiving concomitant lithium, and she died.

Dr. Boehm identified 56 reports of cardiac toxicity (decreased EF or CHF) in patients without a reported MI. Many of these patients had previously received anthracyclines or radiation to the chest, which are accepted as risk factors for the development of cardiac toxicity in patients treated with Novantrone. Dr. Boehm investigated these cases for patients who experienced cardiac toxicity with relatively low cumulative doses of Novantrone, and identified at least 4 such cases (previous exposure to identified risk factors unknown). These cases ranged from markedly decreased EF to cardiac failure (1 death) at doses as low as 10 mg/m^2.

Literature Reports

Dr. Boehm has reviewed several articles from the published literature that examine the risk of cardiac failure with Novantrone treatment in several large cohorts of cancer patients. His detailed discussion of this issue can be found on pages 32-34 of his review; I will very briefly describe below the conclusions reached by the authors of these articles. It is important to note that the number of patients receiving the highest doses in all of these cohorts was small.

One article examined the cumulative risk of CHF in a cohort of 1228 patients. This article describes a cumulative risk of CHF of about 2% up to a cumulative dose of about 120 mg/m^2 in patients not previously treated with an anthracycline. In this cohort, a cumulative dose of greater than 160 mg/m^2 was associated with a steep increase in risk for CHF.

A second article, describing the experience in 774 patients, also revealed a cumulative risk of CHF of about 1-2% up to a dose of 160 mg/m^2 in patients not previously treated with doxorubicin, after which the risk of CHF rose sharply.

A third article, describing the experience of 1211 patients again documented a cumulative risk of CHF of about 2% up to a cumulative dose of 120 mg/m^2, after which the risk rose sharply above a dose of 160 mg/m^2.

A fourth article also described an increase in risk for cardiac toxicity by dose and duration in a cohort of 801 cancer patients.

Other reports in the literature describe cardiac toxicity in cancer patients treated with Novantrone, but do not examine the relationship between cumulative dose and risk.

The sponsor identified 8 literature reports of Novantrone experience in MS patients. Most of these articles describe small numbers of patients treated, and are either silent on risk for CHF, or identify no cardiac toxicity (many do not describe the method of monitoring for these effects).

The largest MS experience reported in the literature, (Gonsett RE, Mitoxantrone Immunotherapy in Multiple Sclerosis, Multiple Sclerosis, 1, 329-332, 1996) describes the treatment of 68 patients. About 12% of patients developed cardiac toxicity (mostly described as decreased EF); the range of cumulative doses was 94-207 mg/m^2. One patient, who received the highest dose, died of heart failure 2 months after her last dose.

Other toxicities known to be associated with Novantrone treatment

Leukemia

It is believed that topoisomerase II inhibitors, including Novantrone, when used in combination with other antineoplastics, are associated with the development of acute leukemia.

According to the sponsor, 2 different types of leukemia may occur. The first is associated with a relatively long latency (3-5 years), has a pre-leukemic phase, and has a poor prognosis. The second type has a relatively short latency (<3 years), a myelocytic or monocytic predominance, and a relatively good prognosis.

As described by Dr. Boehm (page 36 of his review), the sponsor has reviewed 6 publications describing the risk of leukemia in patients treated with Novantrone. These patients were all treated with concomitant antineoplastics, and the risk of leukemia varied from 0.3% to 5%, with latencies ranging from 1.5-6 years. There were no such malignancies seen in the NDA database, although the sponsor describes a case report of an MS patient who received a cumulative Novantrone dose of 87.5 mg/m^2 and developed leukemia 5 years after the last dose.

COMMENTS

The sponsor has presented the results of 2 randomized controlled trials that they believe establish the effectiveness of Novantrone as a treatment that slows the progression of neurologic disability and reduces the relapse rate in patients with progressive multiple sclerosis. In addition, the sponsor concludes that the safety data generated in MS patients, as well as the safety experience gained in patients with other diagnoses, supports the approval of the application.

The application poses a number of interesting issues.

First, we are interested in the Committee's opinion regarding the adequacy of the controlled trials to support the specific claim proposed by the sponsor.

Specifically, do the data support the conclusion that Novantrone slows the progression of neurologic disability and reduces the relapse rate in patients with progressive multiple sclerosis?

When considering this question, it is worth examining the populations enrolled into the trials. In Study 0901, patients with secondary progressive or remittent progressive MS were enrolled. In Study 0902, while the inclusion criteria required that patients have active MS, the vast majority of patients enrolled were diagnosed with relapsing-remitting MS, not progressive MS. Given this, it is fair to ask if the data presented constitute substantial evidence of effectiveness (ordinarily defined as data from at least 2 independent experiments) for any claim in patients with progressive MS.

Certainly, there is precedent for the Division to grant a claim for conditions related to an already approved indication on the basis of a single trial. For example, the Division has granted claims for generalized seizures for an anticonvulsant already approved for partial seizures, and has granted, in effect, a claim for early and late Parkinson's Disease on the basis of a single trial in each setting. In these cases, the principle applied was that the conditions under study were sufficiently related to one another to permit the claims. In the former example, however, the single study on which the additional claim has been granted occurred against a background of independent corroboration of the initial claim, and in the latter example, the same condition was under study.

In the current application, while patients in both trials were diagnosed with MS, they were diagnosed with different forms of MS. While some experts consider that (some of) these nominally different forms constitute a continuum of disease, others consider them to be more distinct, both pathophysiologically, and in their response to treatment. We are very interested in the Committee's views on this matter.

Next, the proposed claims for the specific effects of Novantrone are of interest.

The sponsor proposes that Novantrone slows the progression of neurologic disability, as well as reduces relapse rate.

The Division has been reluctant to grant a claim for the slowing of progression of any degenerative neurologic illness in the absence of a controlled trial that is designed to demonstrate such an effect. Specifically, such a trial would incorporate some variant of a design in which patients originally randomized to active treatment are withdrawn from treatment and whose subsequent course is compared to that of patients originally randomized to, and continuing on, placebo. If the difference in treatment effect seen between active treatment and placebo persists when the active patients are withdrawn from treatment, this would imply an effect on the underlying progression of the disease. In the absence of some design that incorporates such features, any effect seen on, for example, a scale that ostensibly measures function (as the EDSS does in this trial), may simply reflect a symptomatic effect. We are very interested in the Committee's thoughts on this matter.

Also, any putative effect on relapse rate needs to be examined.

In this context, it is critical to recall that these trials were unblinded. Study 0901 utilized a blinded evaluator, while Study 0902 did not (for the clinical outcomes). Recall that in Study 0901, the primary outcome was a combination of 5 measures. Three of these measures were functional scales and 2 measures were related to relapse, Time to First Relapse Treated with Steroids, and the Number of such relapses (presumably, the decision to treat these episodes with steroids was made by the blinded neurologist), and the between treatment comparison for all of these measures reached statistical significance. However, the diagnoses of relapses in Study 0902 were made by neurologists who were aware of the treatment assignments, as were the patients. Although the sponsor reports highly statistically significant results for the between treatment comparison on the number of relapses in this study, we are interested to hear the Committee's views on the effect of unblinding on this outcome. Indeed, we are eager to hear the Committee's overall views of the effects of the knowledge of treatment assignment by the various parties on the clinical outcomes in both studies.

Of course, the primary outcome of Study 0902 was the Percentage of Patients Without New Gd-Enhanced Lesions, an MRI measure, which was highly statistically significant, and this was read by blinded observers.

Again, the Division has been reluctant to base a conclusion on the effectiveness of a product on a measure other than a measure of direct clinical benefit (e.g., a relevant scale measuring functionality, a counting of relevant clinical events, etc). Indeed, I am aware of no instance in which the Division has considered a controlled trial "positive" on the basis of such a measure. This is not the say that the Agency has not done so; such measures are routinely used in some clinical settings, and, specifically, the approval of Betaseron was based, in part, on its effects on MRI.

The use of an MRI measure on which to base a finding of effectiveness raises the important question of the appropriateness of the use of surrogate markers in this setting.

The Agency has incorporated in its regulations (Subpart H of the NDA regulations, so-called Accelerated Approval), and more recently in the Federal Food, Drug, and Cosmetic Act (since 1997), provisions for basing a finding of substantial evidence on controlled trials in which a treatment demonstrates an effect on a surrogate marker (a laboratory or other measure that is not a direct clinical measure). In the absence of true validation of the surrogate (validation would imply that an effect on the surrogate is known to reliably predict the clinical effect of interest), an effect on such a measure must be reasonably likely to predict the drug's effect on the clinical outcome of interest. Reliance on a drug's effect on an unvalidated surrogate as being reasonably likely to predict a future clinical effect is almost always problematic and raises several important questions (it is worth noting that there appears to be general agreement that MRI in patients with MS has not been validated as a surrogate in the sense I have been talking about).

The first issue that must be addressed is whether or not the treatment interferes with the measurement itself. That is, does the treatment interact with the assay system so that the surrogate itself is altered (in this case, for example, is there an interaction between Novantrone and the injected Gadolinium) with no concomitant change in the brain? Then, it is reasonable to ask if there are effects on the brain that are reflected in the surrogate, but that are of no clinical consequence. For example, if generalized atrophy is taken as an MRI surrogate, it is possible to imagine that a treatment may increase brain water, so that the brain may no longer appear atrophic, but such an effect would be of no clinical utility.

This latter may be an example of a more general potential problem with surrogates; that is, the factors influencing the surrogate may not be in the "direct pathway" of the pathophysiologic events giving rise to the disease state; in such a case, the drug may have a "beneficial" effect on the surrogate, but no effect at all on the disease to be treated. In addition, the drug may have an unintended effect on the disease as well as the desired effect on the surrogate, so that the condition may actually be worsened in the face of a "beneficial" effect on the surrogate (some see this more as a safety issue, rather than as a failure of the surrogate, but, in either case, the effect on the surrogate may be misleading). Further, the effect on the surrogate may be short-lived, such that the any effect seen will not be reflected in the predicted long term effect desired on the clinical outcome of interest.

The sponsor's use of the MRI findings, however, while raising the question of its use as a surrogate as defined in the regulations (that is, to predict future clinical benefit), also raises the question of its use as what can be called a contemporaneous surrogate. By this, I mean the use of this specific MRI measure as a reflection of the underlying brain pathology at the time of the scan. When used as this type of surrogate, the claim would be that an effect on the MRI accurately reflects the drug's effect on the underlying brain pathology at that time. In this formulation, the case could be made that a beneficial effect on the surrogate is reflected in an effect on the underlying pathology which could be considered, by definition, beneficial for the patient, even in the absence of a manifest clinical benefit (for example, the lesions seen may be in "silent" brain areas, clinical measures are too insensitive to detect such changes, etc).

When used in this way, though, additional questions are raised.

The first question we can ask is what specific MRI measure reflects what specific brain pathology (and, in particular here, what pathology is reflected in the specific MRI measures used in this study, and what is the evidence for the answer given).

We must further ask if the effect on the surrogate is so small that it can never be reflected in any meaningful clinical benefit (after all, any use of a surrogate must be based on the presumption that it reflects some benefit to the patient). For example, suppose the effect on the MRI reflects the preservation of a very small number of neurons (given its great sensitivity); it is possible that such an effect could never be reflected in a meaningful clinical benefit, regardless of how sensitive such measures could be made. In the typical

case, when clinical measures are used as primary outcomes, we are usually not concerned about the size of the treatment effect seen; we accept, ordinarily, that any effect shown to be statistically significant is worthwhile from a clinical point of view (it establishes proof of principle of the effect of the treatment). Use of a surrogate, however, requires that we consider the size of the effect. This is problematic, because if the clinical effect associated with a particular effect on the surrogate is trivial (or non-existent), and we do not know how to establish this clinical effect, it is difficult to make a risk-benefit decision about the drug.

It should be noted that there is general agreement by MS experts that MRI (at least some measures) accurately reflects underlying brain pathology, and many such experts believe that MRI should be accepted as an adequate surrogate on which to base a decision about the effectiveness of a drug. Given this, given the concerns raised above, and given the outcomes in these trials, we are eager to learn the Committee's positions on the appropriateness of relying on MRI as a primary measure of effectiveness for Novantrone.

Ultimately, of course, we are primarily interested in whether or not the Committee can conclude that the sponsor has submitted substantial evidence of effectiveness of Novantrone for some worthwhile effect for some identifiable population of patients with MS.

If the Committee concludes that effectiveness has been demonstrated, the question of the effective dose needs to be answered. The two controlled trials used markedly different dosing regimens, and the appropriate regimen to be recommended in labeling is not immediately obvious. Ordinarily, the Agency might not require that a particular dosing regimen be shown to be an effective regimen in 2 independent trials; however, in this case, given the potential serious risks (see below), it is worth discussing whether or not the sponsor has submitted sufficient evidence to justify a specific dosing recommendation (in this regard, the relative merits of the 12 mg/m^2 vs the 5 mg/m^2 dose in Study 0901 should be discussed).

Turning to safety considerations, I believe it is fair to say that no safety findings have emerged from the patients in the 2 controlled trials and the German cohort that would preclude approval, though this experience did demonstrate Novantrone's effects on the heart (dose related decrease in Ejection Fraction in Study 0901), hematologic system (decreased WBC and neutrophil counts), GI system (nausea and vomiting), and possibly renal system (dose related increased incidence of UTI).

However, use of Novantrone can be associated with serious toxicity, especially to the heart and bone marrow, and this toxicity is believed to be primarily related to cumulative dose (although the post-marketing experience suggests that CHF can occur at relatively low doses, even possibly after a few doses). As Dr. Boehm notes, most articles in the literature have identified a cumulative risk of CHF of about 2% to 120 mg/m^2, after which the risk seems to rise steeply above about 160 mg/m^2.

Of course, the fundamental question that needs to be answered is whether or not, if the Committee concludes that the sponsor has submitted substantial evidence of effectiveness for some identifiable population, the benefits justify the potential risks. In addition, MS is, of course, a chronic illness, and it is expected that any treatment approved for these patients could be given indefinitely. Indefinite use of Novantrone, however, poses the problem of potentially irreversible, life threatening toxicity. We are particularly interested in the Committee's views of the propriety of permitting indefinite use of Novantrone in patients with MS (assuming the Committee concludes that effectiveness has been demonstrated), or whether limits should be placed on the number of courses of treatment, a highly unusual outcome for a treatment directed at a chronic illness. In addition, we are interested to know if the Committee believes that the use of Novantrone in patients with MS should be restricted to physicians experienced in the use of chemotherapeutic agents, oncologists specifically, or whether or not any other restrictions in its use should be imposed.

While the issues identified in this memo are ones we would like the Committee to address, we are, of course, interested in learning if there are additional issues not discussed here that are of interest to the Committee.

I thank you in advance for all the work you will do prior to the meeting, and for your efforts at the meeting itself. I look forward to an interesting and productive meeting, and to seeing you all on January 28th.

/S/

Russell Katz, M.D.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 24, 1999

FROM: Glenna G. Fitzgerald, Ph.D. /S/ 11/24/99
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA ——
Novantrone (mitoxantrone HCl)
Wyeth-Ayerst
intravenous solution

SUBJECT: Approvability for Pharmacology and Toxicology for multiple sclerosis

---

Novantrone is approved for initial therapy in hormone-refractory prostate cancer and for combination initial therapy in acute nonlymphocytic leukemia. Recommended doses are 12 to 14 mg/m^2 given as a short intravenous infusion every 21 days, and 12 mg/m^2 daily on days 1 - 3 as an intravenous infusion, respectively. The current NDA is for treatment of patients with secondary progressive multiple sclerosis, including progressive relapsing. The recommended dose is 12 mg/m^2 given as a 5 to 15 minute infusion every 3 months.

The toxicology studies that have already been conducted for mitoxantrone support the new indication, even though the duration of treatment in MS patients, who represent a younger population in general than prostate patients, will no doubt be longer. There are carcinogenicity studies, in which mice and rats were dosed intravenously once every 21 days for 24 months, a full battery of genetic toxicology studies, and reproductive toxicology studies (except a pre- and post-natal study). There is also a one year rat study and a 44 week monkey study; in both, dosing was every 21 days. The doses in the toxicology studies were only a fraction of the human dose of 12 mg/m^2 because the animals did not tolerate higher doses. Mitoxantrone is a cytotoxic agent, and caused mortality, neutropenia, decreases in hematocrit and bone marrow hypocellularity, lymphoid depletion, and necrosis in heart, kidney and testes in animals.

Mitoxantrone is both mutagenic and clastogenic (*in vitro* and *in vivo*). It was carcinogenic in the two year studies at doses which represent 0.02 to 0.03 times the human dose for MS on a mg/m^2 basis, and in the one year rat study at 0.15 times the human dose. In the reproduction studies the drug was administered daily, but also at very low doses (0.01 to 0.05 times the human dose based on surface area) and only modest effects were seen. However, Novantrone is labeled Pregnancy Category D based on its mechanism of action (cytocydal effects and DNA reactivity).

Recommendations:

The Pharmacology and Toxicology studies support the chronic use of Novantrone in multiple sclerosis patients.

It is recommended that the current labeling be slightly amended as follows.

1) The following statement should be added to the Carcinogenesis section because it provides evidence for earlier appearance of tumors than would be indicated by the carcinogenicity studies.

2) The following Pregnancy labeling, which differs slightly from the current labeling, is recommended.

Recommended changes in labeling should be cleared with the Division of Oncologic Drug Products.

NDA 21-120
c.c. HFD-120 Div. File
Katz/Roney/Fisher/Fitzgerald/Wheelous

APPEARS THIS WAY
ON ORIGINAL

Immunex

NEW CORRESP

ORIGINAL

November 5, 1999

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

CENTER FOR DRUG EVALUATION AND RESEARCH

NOV 05 1999

RECEIVED HFD-120

RE: NDA 21-120, Amendment No. 007
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
General Correspondence - Minutes of Teleconference

Dear Madam or Sir:

Enclosed please find three copies of an amendment to our application. Please refer to NDA 21-120 submitted on June 4, 1999, and to the teleconference that took place between Immunex and FDA on October 29, 1999. The teleconference was requested to review the status of the NDA review. The Immunex Corporation minutes of the teleconference are attached. In addition, a copy of a facsimile sent to Dr.'s Katz, Lumpkin and Temple on November 3, 1999 is provided. The facsimile contains the Immunex response to the issues raised by FDA regarding the reason the Agency feels that review by the Peripheral and CNS Drugs Advisory Committee is needed. Please provide copies of this submission to appropriate members of the review team. We would appreciate your feedback on the commitments made and can provide additional detail if necessary.

Three copies of this correspondence are attached.

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

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

cc: Nancy Kercher
File 31100, 31543 (NDA 21-120)

MEMORANDUM OF TELEPHONE CONVERSATION
NDA 21-120

Drug: Novantrone i.v. For Multiple Sclerosis
Sponsor: Immunex
Date: October 29, 1999
Conversation Between:

Agency:	Sponsor:
Dr. R. Katz – Acting Division Director	M. Gauthier – Sr. Reg. Affairs Mngr.
Dr. J. Rouzer – Kammeyer – Medical Reviewer	Dr. A. Hayes
Dr. G. Boehm – Safety Reviewer	Dr. K. Seaman
Ms. T. Wheelous – Project Manager	Dr. A. Rubin

Purpose: To discuss the status of the NDA as requested by Immunex in a submission dated October 15, 1999.

Discussion:

I. Review Status of NDA

➡The application is currently under review and progressing well, however the primary reviews are not yet finalized.

➡At this point in the review cycle there are no known major review issues.

II. Need for an Advisory Committee Meeting

MRI Use as Primary Outcome Measure

➡There are several tough questions requiring a public discussion about the use of Novantrone, a toxic oncology agent, in Multiple Sclerosis (MS).

➡One of the two trials conducted by Immunex uses MRIs, a proposed surrogate marker for efficacy as the primary outcome measure.

➡Since this Division has not approved a drug based upon MRI outcomes, and the acceptance of MRIs as a surrogate marker has not yet been adopted by the MS expert community, it is necessary to obtain an advisory opinion regarding the appropriateness of MRIs as an outcome measure in MS.

➡Additionally, an opinion is desired on the use of an open uncontrolled trial where only the MRI reader is blinded.

Dosing Regimen in MS

➡Another topic for discussion will be the dosing regimen for MS. Based upon the two trials conducted, the dosing regimen that is associated with MRI effects is different from the dosing regimen used in the trial with a primary clinical endpoint.

Chronic use with a Drug that has Maximum Total Dose

➡The current Novantrone labeling does not have a maximum cumulative dose, but a dose of [redacted] is proposed [redacted]

Risk vs. Benefit Concerns

➡Given the known toxicities of this drug and considering the risk vs. benefit, the advisory committee will be asked to consider whether or not approval is warranted, and, if so, what the appropriate dose regimen should be.

➡Immunex believes that except for transient neutropenia patients do well in regard to toxicity. However, animal carcinogenicity data associates Novantrone with numerous toxicities and toxicities may be cumulative with repeat dosing as proposed in MS.

➡Since MS patients will require long time (lifetime) treatment, it is necessary to know the trend in adverse effects with cumulative dosing.

➡The sponsor would like to be informed of the Division's action decision prior to the issuance of the action letter at least three days before. The reason for this request is so that the sponsor can decide whether or not to withdraw the application. Immunex was informed that regardless of the action taken by the Division, this drug would still be presented to an Advisory Committee.

➡The specific issues that will be discussed at the Advisory Committee Meeting will be outlined in the action letter sent to the sponsor prior to the meeting. Currently, the Division is not permitted to share the Division's meeting package with the sponsor, but the Division is willing to meet with the sponsor prior to the Advisory Committee Meeting in order to discuss all of the discussion items.

/S/

Teresa Wheelous, RPh

cc: Orig NDA 21-120
HFD-120
/Katz
/Wheelous /S/
/Rouzer
/Boehm
Draft: November 2, 1999
Final:
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APPEARS THIS WAY
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DRUG AMENDMENT

October 26, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

OCT 27 1999

RECEIVED HFD-120

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. 006
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Response to Request for Information

Dear Madam or Sir:

Please refer to NDA 21-120 submitted on June 4, 1999, your facsimile dated September 8, 1999, and to our September 27, 1999 response. In the September 27 submission, Immunex provided an unofficial translation of the CRF for Patient No. 304 in Study 031.0902. Attached please find a copy of the certified translation of the CRF for Patient No. 304. Three copies of this submission are enclosed – one archival copy, one review copy and one desk copy.

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

Sincerely,

Mark W Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

cc: Nancy Kercher
File 31100, ~~31543~~ (NDA 21-120)

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

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

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DATE:	**October 7, 1999**
TIME:	**11:00 AM**
DELIVER TO:	Mark Gauthier
Fax Number:	(206) 223-0468
Phone Number:	

APPEARS THIS WAY
ON ORIGINAL

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

Total number of pages, including cover page: 2(1-cover page)

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

MESSAGE:
Mark,
The following is a list of information requests from the safety reviewer for Novantrone, NDA 21-120:

1 In study 013.091, the dose of mitoxantrone was adjusted based on toxicity. You have provided information about the number of subjects who had their dose adjusted and the number of adjustments for each of these subjects. When you provided the reason for dose adjustment it was either attributed to hematologic toxicity or non-hematologic toxicity (Listing: Dose adjustment vol. 88, p.89). For each subject who had a dose adjustment for toxicity, please provide the specific reason for dose adjustment. For example, if the dose adjustment was for non-hematologic toxicity then state the actual event (nausea, lab abnormality with the lab result, diarrhea). If the dose adjustment was for hematologic toxicity, then identify the abnormality and provide the lab result that led to the adjustment.

2 I have not identified any cases of neutropenic fever in the NDA phase II and Phase III trials please confirm that no such events occurred.

3 You stated that in the phase II trial there was no evidence from the echocardiographic examinations of cardiotoxicity. Does that mean that no patients experienced a decrease in EF of 10% from baseline?

4 Your current labeling states that the stomatitis cases occurred within 1 week of therapy. Please verify that time frame for the subjects treated with mitoxantrone in the MS Phase II and III trials.

5 In your 9/27/99 submission, you confirmed that different units were used for various lab tests in the Phase III trial and that these were converted prior to analyzing the data but were not converted for the lab listings (Q7, vol. 1, p.16). Corrected lab listings were not provided with the 9/27/99 submission. In reviewing table 12.3.3.-11 on p. 190 vol. 86 of the NDA submission, the MAX for creatinine illustrates that during the study there were creatinines in the [redacted] range in all treatment groups. Table 12.3.3.-12 (p. 191, vol. 86) documents that there were bilirubins as high as [redacted] Using the corrected lab values, please provide a listing that identifies all patients with a creatinine greater than 2.0mg/dL at any time during the study. For these patients with a creatinine >2.0mg/dL, provide all of their creatinine results during the study. Similarly, please provide a listing that identifies all patients with a bilirubin greater than 2.0mg/dL at any time during the study, and all of their bilirubin results during the study.

Thanks,
Teresa

APPEARS THIS WAY
ON ORIGINAL

immunex

N(BM)
ORIG AMENDMENT

ORIGINAL

October 14, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 15 1999
RECEIVED HFD-120

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. 005
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Response to Request for Information

Dear Madam or Sir:

Please refer to NDA 21-120 submitted on June 4, 1999 and to your facsimile dated October 7, 1999 that provided additional comments from the safety reviewer. This submission (3 copies provided – 1 archival copy, 1 review copy, and 1 desk copy) addresses all of the comments from the safety reviewer. In addition, a corrected page for Final Clinical Study Report 031.0901, Section 12.4.1 and updated safety information for Patient No. 5905 who became pregnant while receiving mitoxantrone in Study 031.0901 are provided.

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

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31543 (NDA 21-120)

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

Immunex Corporation

Immunex

October 1, 1999

ORIGINAL

N(84)

ORIG AMENDMENT

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

CENTER FOR DRUG EVALUATION AND RESEARCH

OCT 04 1999

RECEIVED HFD-120

RE: NDA 21-120, Amendment No. 003
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Item 9: Four Month Safety Update

Dear Madam or Sir:

Please refer to NDA 21-120 submitted on June 4, 1999. Enclosed please find 3 copies (1 archival, 1 review and desk copy) of the 4-month safety update for NDA 21-120. Of note, on Tuesday, September 28, 1999, Immunex forwarded a response to questions from the safety reviewer. This response included subject summaries for 20 patients from the 031.0903 study who died. After the submission was sent, a number of typographical errors were discovered in the summaries, such as the inadvertent substitution of "methotrexate" where "mitoxantrone" should have been indicated, as well as more minor editorial changes. Copies of the corrected subject summaries are included in this submission and they are now accurate.

SAS datasets for the month 36 timepoint are included in the archival and review copies but not in the desk copy.

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

Sincerely,

Mark W. Gauthier
Senior Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

cc: Nancy Kercher
File 31100, 31543 (NDA 21-120)

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

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NEW CORRESP

NC

ORIGINAL

September 29, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

SEP 30 1999

RECEIVED HFD-120

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
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
General Correspondence – Plans for Pediatric Drug Development

Dear Madam or Sir:

Please refer to NDA 21-120 submitted on June 4, 1999 and to your letter of July 26, 1999. In the July 26 letter, FDA requested that Immunex either notify the Agency of our plans for pediatric drug development for Novantrone or request a waiver of the pediatric study requirement. Immunex Corporation believes that Novantrone qualifies for a waiver of the pediatric study requirement for two of the indications listed below – prostate cancer (NDA 19-297) and secondary progressive multiple sclerosis (NDA 21-120); justification provided below. However, acute nonlymphocytic leukemia is known to occur in pediatric patients although in very small numbers (approximately 400-500 patients per year). These patients may potentially benefit from Novantrone treatment. We are aware of two peer reviewed published studies which could be used to support revised labeling to address pediatric use.

NDA 19-297

1. *NOVANTRONE in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.* Prostate cancer is included in the list of diseases that are unlikely to occur in pediatric populations that appears in the publication of the Final Rule in the Federal Register Notice of December 2, 1998. The preamble to the rule states that an applicant requesting a waiver should reference the Federal Register Notice in their waiver request.

APPEARS THIS WAY
ON ORIGINAL

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

2. *NOVANTRONE in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic monocytic, and erythroid acute leukemias.* As discussed above, ANLL does affect pediatric patients although in a very limited patient population. Immunex commits to propose a filing strategy based on the published literature reports cited above with the Division of Oncology Drug Products by October 31, 1999. A copy of this letter will be sent to Dr. Richard Pazdur, Director, to alert him to our tentative plans.

NDA 21-120 –

Proposed indication: *NOVANTRONE is* [redacted]

[redacted]

[redacted]. Novantrone has been designated as an orphan drug for the secondary progressive and progressive relapsing indications effective August 13, 1999 (refer to applications # 99-1284 and 99-1251, Office of Orphan Products Development, HF-35). As stated in to the preamble to the Final Rule published in the Federal Register Notice of December 2, 1998: "The final rule does not, however, require the submission of pediatric data for a drug for an indication or indications for which orphan designation has been granted under section 526 of the Federal Food, Drug, and Cosmetic Act..."

I assume this response adequately addresses the issue raised in your letter of July 26, 1999 regarding our plans for pediatric drug development for this product.

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

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31543 (NDA 21-120)

APPEARS THIS WAY
ON ORIGINAL

IMMUNEX

September 27, 1999

ORIG AMENDMENT
N-(BM)
ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

SEP 29 1999

RECEIVED HFD-120

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
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Response to Request for Information

Dear Madam or Sir:

Please refer to NDA 21-120 submitted on June 4, 1999 and to your facsimile dated September 8, 1999 that provided comments from the safety reviewer. This 19 volume submission (2 copies provided) addresses all of the comments from the safety reviewer, including copies of the CRFs for all patients who experienced a serious adverse event (SAE). The first volume contains responses to the comments, subject summaries, etc. Volumes 2-19 contain copies of the CRFs for those patients.

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

Sincerely,

Mark W. Gauthier
Senior Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

cc: Nancy Kercher
File 31100, 31543 (NDA 21-120)

immunex

ORIG AMENDMENT

September 10, 1999

ORIGINAL 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

CENTER FOR DRUG EVALUATION AND RESEARCH

SEP 13 1999

RECEIVED HFD-120

RE: NDA 21-120, Amendment No. 002
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Corrections to Clinical Study Report

Dear Madam or Sir:

Please refer to NDA 21-120 submitted on June 4, 1999. After submission of the NDA, a number of minor errors were discovered in the Final Clinical Study Report for Study 031.0901. Enclosed please find corrected pages to be used to replace the current pages in the report. Most of the corrections were to the SmarTest output tables. The corrections were effective August 23, 1999. Listed below are the pages to which corrections were made and the page number where they are located in the Clinical Study Report.

Clinical Study Report Page No.	Table No.	Overall Vol. No.	Page No as it appears in the NDA
55	11.3.1.1	86	Item 8, Vol. 003-Page 055
58	11.3.1.2.1.C	86	Item 8, Vol. 003-Page 058
59	11.3.1.2.2.C	86	Item 8, Vol. 003-Page 059
61	11.3.1.2.3.D	86	Item 8, Vol. 003-Page 061
62	11.3.1.2.4.B	86	Item 8, Vol. 003-Page 062
63	11.3.1.2.5.C	86	Item 8, Vol. 003-Page 063
78	11.3.2.4	86	Item 8, Vol. 003-Page 078
118	12.4.1.1	86	Item 8, Vol. 003-Page 118
Appendix VII	A 11.3.1-1	87	Item 8, Vol. 004-Page 051 – 056

The changes listed above affected only the information within the tables referenced. They did not result in any changes to the accompanying text. An Errata sheet listing each of the changes and reason for the change precedes the corrected pages. Three copies of this submission are provided – one for the archival copy of the NDA, one to replace the corresponding pages in Item 8, and an additional copy for insertion in Item 10.

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In addition, a copy of the cover letter of a recent submission to Dr. Matthew Thomas, HFD-344, is provided to update the file.

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

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31543 (NDA 21-120)

APPEARS THIS WAY
ON ORIGINAL

immunex

ORIG AMENDMENT

September 10, 1999

ORIGINAL 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

CENTER FOR DRUG EVALUATION AND RESEARCH

SEP 13 1999

RECEIVED HFD-120

RE: NDA 21-120, Amendment No. 002
New Drug Application for NOVANTRONE®
(mitoxantrone for injection concentrate)
Corrections to Clinical Study Report

Dear Madam or Sir:

Please refer to NDA 21-120 submitted on June 4, 1999. After submission of the ND number of minor errors were discovered in the Final Clinical Study Report for Study 031.0901. Enclosed please find corrected pages to be used to replace the current pag the report. Most of the corrections were to the [redacted] output tables. The correcti were effective August 23, 1999. Listed below are the pages to which corrections wer made and the page number where they are located in the Clinical Study Report.

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Appendix VII	A 11.3.1-1	87	Item 8, Vol. 004-Page 051 – 056

The changes listed above affected only the information within the tables referenced. They did not result in any changes to the accompanying text. An Errata sheet listing each of the changes and reason for the change precedes the corrected pages. Three copies of this submission are provided – one for the archival copy of the NDA, one to replace the corresponding pages in Item 8, and an additional copy for insertion in Item 10.

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206.587.0430, Fax 206.587.0606 www.immunex.com

51

Immunex Corporation

immunex

August 13, 1999

ORIGINAL (NCBS)

ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

AUG 16 1999

RECEIVED HFD-120

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. 001
New Drug Application for NOVANTRONE
(mitoxantrone for injection concentrate)
Response to Request for Information

APPEARS THIS WAY
ON ORIGINAL

Dear Madam or Sir:

Please refer to NDA 21-120 submitted on June 4, 1999. The following items are provided in response to requests from the Statistical Reviewer, Dr. Sharon Yan, to aid in her review of NDA 21-120:

1. Diskette containing SAS efficacy data of intermediate measurements (every three months) organized such that each patient has multiple lines with one record per patient every three months, except for relapses. There are variables to record the chronology of relapses in six month intervals. A more detailed explanation of the SAS datasets is included with the diskette. This is in response to the e-mail from the Project Manager dated 7/21/99 (Study 31.0901).

2. Additional analyses were requested during a meeting between FDA and Immunex statisticians on 8/5/99. These are: analyses at each 3 month evaluation of trends over time for primary and important secondary endpoints, and additional subset analyses by age and gender for the 5 primary endpoints in Study 31.0901 and for the single primary endpoint in Study 31.0902.

Regarding Item 1 above, during the meeting on 8/5/99, a copy of the SAS datasets as described above was provided to Dr. Yan. An archival copy of the diskette is provided with this submission since Dr. Yan already has a copy for use during her review.

51 University Street, Seattle, Washington 98101-2936

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

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31543 (NDA 21-120)

APPEARS THIS WAY
ON ORIGINAL

Immunex Corporation

June 8, 1999

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Woodmont II Building, 4th Floor
1451 Rockville Pike
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

Attn: Ms. Teresa Wheelous

RE: NDA 21-120
New Drug Application for NOVANTRONE
(mitoxantrone for injection concentrate)
General Correspondence – Response to FDA Request

Dear Madam or Sir:

Provided with this letter are 4 additional desk copies of Volume 1 of NDA 21-120. The desk copies are provided in response to a request from the Project Manager, Ms. Teresa Wheelous by telephone on June 7, 1999. Volume 1 contains the following items: Form 356h, Index (Item 1), Draft Labeling (Item 2), Application Summary (Item 3), Patent Information (Items 13 & 14), and Debarment Certification (Item 16).

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

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

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

immunex

June 2, 1999

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Woodmont II Building, 4th Floor
1451 Rockville Pike
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 21-120
New Drug Application for NOVANTRONE
(mitoxantrone for injection concentrate)

Dear Madam or Sir:

Pursuant to 21 CFR 314.50, Immunex Corporation is submitting a New Drug Application (NDA) to request approval of a new indication for the product, NOVANTRONE, mitoxantrone concentrate for injection. The additional indication being sought is:

[redacted]

Results are presented from a randomized phase III clinical trial (31.0901) that demonstrates that Novantrone provides a significant benefit in patients with secondary progressive and relapsing-progressive forms of multiple sclerosis. Results from a randomized phase II trial (31.0902) are also included that support the results of the pivotal trial. Final clinical trial reports for the pivotal study (31.0901) and the supportive study (31.0902), including all data tabulations and listings, are located in Items 8 & 10 of this submission, respectively. A third report (31.0903) is provided that describes an analysis of long-term safety data collected retrospectively from 454 patients treated with Novantrone from November 1988 – September 1998 at a single center. Final clinical study report, data tabulations and listings are also provided in Items 8 & 10. Please refer to the table of contents for a detailed listing.

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206.587.0430, Fax 206.587.0606 www.immunex.com

IMMUNEX

The Chemistry, Manufacturing and Controls section of NDA 21-120 consists of a copy of a supplement (NDA 19-297/S-017) submitted on May 6, 1997 and approved on August 13, 1998 which provided for an alternate supplier of the bulk drug substance. Use of the CMC supplement was previously agreed to by the Chemistry Team Leader for Neuropharmacological Drug Products in the Division of New Drug Chemistry. S-017 included a reference to the Drug Master File for manufacture of the drug substance, stability data on the drug substance and product, methods used for analysis, etc. Since this supplement was previously approved by the Division of Oncology Drug Products, it was also agreed that Immunex only need submit a copy of the Application Summary (Item 3) to the FDA District Office in San Juan, Puerto Rico, as the Field Copy.
The NDA is paginated according to an Item relative system. Each section (CMC, Nonclinical Pharmacology and Toxicology, Human Pharmacokinetics and Bioavailability, Clinical, and Statistical) is paginated as follows: **Item No.- Vol. No. Page No.**, i.e., the first page of the first volume of the CMC section is numbered as Item 4 – Vol. 1 page 001. Each volume is numbered from 1-400 (maximum), so the first page of volume 2 of the CMC section would be Item 4 – Vol. 2 Page 001. This process is repeated for all of the other sections (Items 5, 6, 8, and 10).

Electronic SAS datasets for the phase II and III studies, 31.0902 and 31.0901, respectively, for use by the Statistician, are also provided in Item 10 of the NDA. Refer to the first volume of Item 10 for the dataset documentation and diskette provided. By prior agreement, any questions on the statistical section can be directed to Dr. Abbe Rubin, Biometrics, at (206) 389-4073. All other communications regarding this NDA will be coordinated through the Project Manager by Immunex.

The safety update (Item 9) will be filed 4 months from the date of submission of this supplement and will include data from the third-year follow up from study 31.0901, as discussed at the April 15, 1999 pre-NDA meeting.

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

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
IMMUNEX CORPORATION	06/02/99
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(206) 587-0430	(206) 223-0468

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	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	Immunex Corporation Tel. 206-587-0430 51 University Street FAX 206 223-0468 Seattle, WA 98101

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS 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)
see attached	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
injectable	20 mg, 25 mg, 30 mg (2 mg/mL)	intravenous

(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 ANDA, 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
New Indication

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.

See attached

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

NDA 19-297, IND

Number of Pages Redacted 47

❖❖❖

Draft Labeling
(not releasable,

(B)

MEETING MINUTES

MEETING DATE: April 12, 1999
IND & DRUG NAME: ——— Novantrone (mitoxantrone)
SPONSOR: Immunex Corp.
TYPE OF MEETING: **Pre-NDA Meeting**

FDA Attendees & Titles:

Dr. R. Katz – Acting Division Director
Dr. G. Williams –Team Leader, HFD-150
Dr. J. Rouzer-Kammeyer – Medical Reviewer
Dr. V. Tammara– Biopharm Reviewer
Dr. G. Fitzgerald – Pharmacology Team Leader
Dr. P. Roney– Pharmacology Reviewer
Dr. M. Guzewska – CMC Team Leader
Dr. T. Broadbent – CMC Reviewer
Dr. Jin – Biometrics Team Leader
Dr. S Yan – Biometrics Reviewer

Immunex Corp. Attendees & Titles:

M. Gauthier, Sr. Mngr. Regulatory Affairs
Dr. A. Rubin – V. P. Biometrics
Dr. R. Ghalie – Medical Director, Clinical Development
Dr. M. Butine – Biometrics
Dr. K. Seamon – Sr. V. P. Drug Development

MEETING OBJECTIVES:

Discuss the necessary components for a type 6 NDA, 21-120, for the use of Novantrone to slow neurological impairment and to reduce the risk of exacerbation in patients with secondary progressive Multiple Sclerosis (M.S.), including relapsing progressive. Novantrone, an approved drug, was originally reviewed and approved by the Division of Oncology for prostate cancer. The sponsor plans to market the same product with the necessary labeling changes to include the treatment of slowing the neurological impairment to reduce the risk of exacerbation in patients with secondary progressive multiple sclerosis, an orphan indication.

DISCUSSION POINTS:

IMMUNEX QUESTIONS:

1. **Confirm that the proposed NDA Table of Contents is acceptable.**

   ▪The proposed data package appears to be acceptable.

2. **Confirm that the proposed insert related to MS indication encompasses appropriate information. Text will be integrated into current approved package insert.**

   ▪ The package insert will be a collective effort between the Division of Oncology Drug Products and the Division of Neuropharmacological Drug Products.

APPEARS THIS WAY
ON ORIGINAL

3. **The NDA will officially be a paper submission, however, electronic reviewer aids can be provided, including: PDF version of final clinical study reports, ISS, ISE, Item 3 Application Summary, and Word version of PI. SAS datasets will be provided for the Statistical review. No hyperlinks.**

   ▪ A paper submission is acceptable.

4. **Confirm that it will be acceptable for the statisticians to contact each other directly to resolve issues related to data handling and analysis.**

   ▪The Agency statistician agrees to be accessible for questions and discussions concerning statistical issues, only. The project manager should be contacted for all other concerns including the status of the application.

5. **In serial No. 006 dated January 15, 1999, we requested a waiver from compliance with the Financial Disclosure Revised Final Rule (21CFR 54). The Phase III trial was completed prior to February 2, 1999, and as such, appears to be exempted from the requirement to provide financial disclosure information from the clinical investigators. Please confirm that this is acceptable.**

   ▪Based upon the Division's understanding of the Financial Disclosure Final Rule, it appears that financial disclosure information from the clinical investigators is not needed as part of the application.

6. **Confirm that inclusion of approved (by the Division of New Drug Chemistry / Oncology Drug Products) CMC information is only for purposes of review of this NDA and that future CMC supplements will not require review and approval from both the Division of Neuropharmacological Drug Products and Oncology drug Products. Recommend that future CMC sNDAs be submitted to Oncology for approval.**

   ▪After action on the new type 6 NDA by the Division of Neuropharmacology, it is appropriate and preferred that all CMC supplements be submitted to the Division of Oncology for review. A copy of the cover letter for each submission should be sent to the Division of Neuropharmacological Products. However, adverse event reporting should be submitted to both Divisions.

<u>SAFETY DATA</u>

▪ All lab values (kidney, liver, blood, chemical) are needed, not just hematologic values. The M.S. patient population is different than the population of patients in which this product is approved. Because of this difference the risk/benefit ratio must be fully explored and assessed.

▪The sponsor should make the case that safety data available from other disease studies are supportive of the safe use of Novantrone in the M.S. population.

▪Immunex intends to use two European trials to support the M.S. effectiveness claim. Immunex acquired one of the trials after the study was completed. Subsequent to the study acquisition Immunex conducted a retrospective data collection search. A detailed explanation of the retrospective data collection should be incorporated into the NDA.

▪The sponsor should make the case that the European M.S. population that participated in the trial is similar to the American M.S. population. For example, the two populations should exhibit the same disease progression as reflected by the concomitant medications taken prior to the administration of Novantrone.

▪Since almost 100% of patients on Novantrone develop neutropenia the sponsor should be sure to address the incidence of fever in neutropenia in the M.S. trials.

▪In the current Novantrone labeling there is a warning that Novantrone "should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents." Since most neurologists do not have experience in chemotherapeutic agents, labeling will have to be created specific to neurologists, and should include information about the rate of fever in neutropenia, and the rate of infusion as supported by the M.S. clinical trials.

▪There may be a need to take this to the Advisory Committee because there will be no U.S. effectiveness data and the drug's toxicities that may discourage it's use in this patient population.

▪The effectiveness database consists of a total of 81 (60 and 21) patients. Since this database is small, additional data will be needed from the approved NDA database.

▪Dose by duration and population is of concern and the ICH guidelines should be consulted.

STATISTICAL CONCERNS:

▪The protocol specified primary analysis should be provided.

▪The primary endpoint for the study conducted in Germany consists of a composite endpoint. Provide enough details about the analysis to allow verification and reproduction of results. If possible provide the Agency with the program and software used to evaluate the analysis. Also provide documentation validating the program.

▪The trend of treatment induced improvement should be substantiated with data. This is especially important for labeling reasons because if effectiveness between the lower dose (5mg/m^2) is comparable to the higher dose (12 mg/m^2) then the lower dose will be recommended in labeling.

▪If the vast majority of positive data appears to be derived from one center or from one country then this disparity should be addressed.

PRE-CLINICAL CONCERNS:

▪Carcinogenicity and Reproductive Studies:

▪Full study reports are needed for both carcinogenicity and reproductive studies. If the studies are judged to be inadequate to support this chronic indication which includes women of childbearing potential, additional studies may be required for an NDA.

▪Both carcinogenicity and reproduction studies, which support the marketed indication, were conducted at doses comparatively lower than the proposed human doses for M.S.

▪Novantrone is currently labeled as category D for pregnancy. We would like to reflect in labeling the data supporting the pregnancy category selected.

▪The toxicology studies conducted are not what are normally required for this indication, but there is no advantage in redoing them since they define immunosuppression as the primary toxicity.

▪Post market analysis and reporting for the approved indication is necessary. Novantrone may be carcinogenic (secondary leukemia occurs in this class of agents) and the post market analysis will be helpful in assessing long-term effects.

KINETICS AND METABOLISM

▪The current standard is to characterize metabolism in humans and not just animals as offered by the sponsor.

▪There is some pK data available for doses of 15 mg/m^2 – 19 mg/m^2, but not at the proposed doses of 5 mg/m^2 and 12 mg/m^2. The sponsor should provide human characterized metabolism data at the doses proposed.

▪Additionally, the sponsor is reminded to supply the biopharmaceutical information requested in the November 1998 meeting. Specifically, please provide: (1) P450 interaction studies (2) gender studies (3) drug-drug interaction studies (4) metabolic pathways to include oxidation reactions, and be sure to address hepatic impairment which can lead to a 3-fold elevation of the AUC.

▪Immunex should refer to Agency guidance documents, e.g. Drug-Drug Interaction Guidance, for assistance.

DECISIONS REACHED:

1. Immunex will consider the points offered by the Agency.
2. Immunex plans to submit a NDA to HFD-120 for M.S. and a labeling supplement containing the M.S. indication with the appropriate changes to The Division of Oncology in late May 1999.

Signature, minutes preparer:

Concurrence Chair:

Cc:
IND ———
HFD-120
HFD-120/R. Katz
HFD-120/J. Rouzer-Kammeyer
HFD-120/G. Fitzgerald
HFD-120/P. Roney
HFD-120/M. Guzewska
HFD-120/T. Broadbent
HFD-860/R. Baweja
HFD-860/v. Tammara
HFD-710/K. Jin
HFD-710/S.Yan
HFD-120/T. Wheelous

APPEARS THIS WAY
ON ORIGINAL

Draft: C:\wheelous\ ——— \pre-NDAmgtmin

PRE-NDA MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

MEETING DATE: November 2, 1998
IND & DRUG NAME: ———— Novantrone (mitoxantrone)
SPONSOR: Immunex Corp.
TYPE OF MEETING: End of Phase II Meeting

ATTENDEES

FDA Attendees & Titles:

Dr. P. Leber – Division Director
Dr. R. Katz – Group Leader
Dr. J. Rouzer-Kammeyer – Medical Reviewer
Dr. G. Fitzgerald – Pharmacology Team Leader
Dr. E. Li – Pharmacology Reviewer
Dr. Baweja – Biopharmaceutics Team Leader
Dr. Zhao – Biopharm Reviewer
Dr. Jin – Biometrics Reviewer
Dr. S Yan - Biometrics

External Participant Attendees & Titles:

M. Gauthierier, Sr. Mngr. Regulatory Affairs
Dr. A. Rubin – V. P. Biometrics
Dr. R. Ghalie – Medical Director, Clinical Development
Dr. K Seaman – Sr. V. P., Drug Development
O. Zenker – Project leader Wyeth Ayerst Germany
Yvonne Lanzendorfer – Assoc., Reg. Affairs
Dr. H. Panitch – Professor of Medicine, University of Maryland
A. Hoyes – Sr. VP, Medical Development

APPEARS THIS WAY
ON ORIGINAL

MEETING OBJECTIVES:

The sponsor, Immunex Corporation, plans to submit a supplemental NDA to the Division for review of the approved cancer product, Novantrone (mitoxantrone hydrochloride) for injection. This supplement will provide for a new indication, the treatment of Multiple Sclerosis (MS). Immunex Corporation would like to (1) obtain FDA concurrence on the adequacy of the design and endpoints of the proposed phase III trial (NO-MS3) and (2) confirm that the activity and safety profile of mitoxantrone as reported in the phase III trial support the label expansion of mitoxantrone for the treatment of patients with Multiple Sclerosis.

DISCUSSION POINTS:

1. **Concur that the population of patients with progressive MS benefit from treatment with mitoxantrone.**

   ▪Upon review of the data from the trials it will be decided if MS patients benefit from mitoxantrone. Based upon the information presented there appears to be reasonable evidence to believe that there is some benefit for MS patients.

▪The proposed phase III study should clearly state the primary endpoint prospectively.

▪From a pre-clinical perspective the sponsor should more fully develop chronic use studies. Be sure to include carcinogenicity data in the supplement (although previously submitted to the original NDA).

▪Biopharmaceutics requires: (1) P450 interaction studies (2) gender studies (3) drug-drug interaction studies (4) metabolic pathways to include oxidation reactions, and be sure to address hepatic impairment which can lead to a 3-fold elevation of the AUC. The sponsor will provide the metabolic data from animals.

2. **Concur that a mitoxantrone dose of 12 mg/m² every 3 months is appropriate for treatment of patients with MS.**

▪The sponsor proposed a low dose long-term (2 years) administration in MS treatment. Low-dose Novantrone studies in prostate cancer have been conducted and safety data is available from these studies.

▪Regarding the length of time of usage, labeling will state only the conditions under which the studies are conducted, i.e., if a two-year study is conducted then labeling will state the results found in a 2 year study.

3. **Confirm that the activity and safety of mitoxantrone support the label expansion of mitoxantrone in MS.**

▪This is a review matter.

▪If all of the trials are positive and there are no contrary results or evidence of use being associated with intolerable adverse events (e.g., aplastic anemia, etc.) then the there should not be a problem indicating mitoxantrone for use in MS.

4. **Confirm that the published data from the two Phase II randomized trials are supporting evidence of mitoxantrone activity in relapsing-remitting MS.**

▪Ordinarily, a minimum of two trials are required for approval of a new indication, however, exceptions are made to accept one trial along with overwhelming supporting evidence.

▪Full data to include protocols, patient records, and all reports of relevant studies from these two phase II randomized trials should be provided for review before the acceptability of the evidence can be determined.

▪The sponsor should obtain the right of reference or ownership of these trials and submit the protocol and data from these trials to the Agency for review. Literature articles and published reports are unacceptable.

5. **Confirm that 1-point deterioration of EDSS at 3 and 6 months can be presented as additional evidence of activity in MS.**

▪This is a review matter.

6. **Confirm that sNDA filing is eligible for priority review.**

▪Priority reviews are granted to applications for drugs based on an estimate of the drugs therapeutic preventive or diagnostic value. Priority drugs should exhibit a significant improvement compared to marketed products in the treatment or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new sub-population.

▪There are currently several products available for MS treatment and given the known toxicity of anti-cancer agents the benefit to MS patients should be substantial relative to the risk and to the products currently available.

▪At this time the classification of the application, standard vs. priority, is undecided.

APPEARS THIS WAY
ON ORIGINAL

DECISIONS REACHED:

1. Sponsor may conduct the proposed studies.
2. Sponsor will provide the pharmacology and biopharmaceutics requests, as stated above, in the future efficacy supplement.
3. Sponsor will request a pre-NDA meeting in the first quarter of 1999.

Signature, minutes preparer:

Concurrence Chair:

Cc:
IND ———
HFD-120

HFD-120/R. Katz
HFD-120/J. Rouzer-Kammeyer
HFD-120/G. Fitzgerald
HFD-120/E.Li
HFD-120/M. Guzewska
HFD-120/T. Broadbent
HFD-860/R. Baweja
HFD-860/H.Zhao
HFD-710/K. Jin
HFD-710/S.Yan
HFD-120/T. Wheelous

APPEARS THIS WAY
ON ORIGINAL

Draft: 12/9/1998
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