

MEMORANDUM

DATE: January 2, 2000

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

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

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/m², 5 mg/m², 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/m ²	Nov 12 mg/m ²
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/m² 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/m² in the high dose group and 37 mg/m² in the low dose group. The highest cumulative dose achieved in this study was 96 mg/m², 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
Arrhythmia	8	6	18
Gamma GT Increased	3	3	15
EKG abn'l	3	5	11
Sinusitis	2	3	6
Granulocytopenia	2	6	6
WBC abn'l	2	8	6
Anemia	2	9	6

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 $2 \times 10^9/L$ at any time. No patient had a neutrophil count below $0.5 \times 10^9/L$. 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%

Study 31.0902

Exposure

The mean cumulative dose in this study was about 81 mg/m², with a range of 62-101 mg/m² (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)

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 $2.0 \times 10^9/L$, and none had a count below $1 \times 10^9/L$ at any time. A total of 19 Novantrone patients (90%) had a neutrophil count of less than or equal to $1 \times 10^9/L$ at least once during the trial, and 9 (43%) had at least one neutrophil count below $0.5 \times 10^9/L$ during the trial. All but 3 of these latter patients had neutrophil counts greater than $0.5 \times 10^9/L$ at the next measurement one week later. No subject (although there were some missing values) had neutrophil counts less than $0.5 \times 10^9/L$ 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 $< 1 \times 10^9/L$	% with Count $< 0.5 \times 10^9/L$
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 heart 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/m² 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/m², and the mean cumulative dose was about 44 mg/m². A total of 93% of patients (424/454) received a cumulative dose of less than 100 mg/m², with the greatest cumulative dose being about 183 mg/m². 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 + cardiomyopathy.

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/m² 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/m²; 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/m². Details were presented only for those patients who died. One was a 42 year old man treated with a cumulative dose of 91 mg/m² 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/m² 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 rhabdomyolysis, 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 rhabdomyolysis 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/m² 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/m².

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/m² in patients not previously treated with an anthracycline. In this cohort, a cumulative dose of greater than 160 mg/m² 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/m² 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/m², after which the risk rose sharply above a dose of 160 mg/m².

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/m². 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/m² 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 relapsing-remitting 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 to 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/m² vs the 5 mg/m² 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/m², after which the risk seems to rise steeply above about 160 mg/m².

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.

Russell Katz, M.D.

