

EXECUTIVE SUMMARY

Study Drug: NOVANTRONE® (Mitoxantrone HCl)

Company: Immunex Corporation

Requested New Indication in Patients with Progressive Multiple Sclerosis:

Demonstrated Benefit To slow progression of neurological disability and reduce the relapse rate in patients with progressive multiple sclerosis.

Requested Dose and Schedule 12 mg/m² every 3 months by short intravenous infusion.

Approved Indications:

- Adult acute nonlymphocytic leukemia (1987), for induction and consolidation therapy at a dose of 12 mg/m²/day x 3 days, repeated every 3-6 weeks.
- Symptomatic hormone refractory prostate cancer (1996), for treatment of pain related to cancer at a dose of 12-14 mg/m², repeated every 3 weeks.

Background and Rationale

Mitoxantrone, an anticancer drug marketed in the U.S. since 1987, has also been investigated as an immunosuppressive agent in the management of patients with multiple sclerosis (MS). Promising results from animal studies of experimental allergic encephalomyelitis (EAE) led to open-label studies of mitoxantrone in MS conducted in the late 1980s. In these initial studies, mitoxantrone doses ranged from 8 to 14 mg/m², with an interval between courses ranging from every 3 weeks to every 3 months. These studies showed that mitoxantrone had manageable side effects in patients with MS, that longer intervals between courses were usually better tolerated, that some patients may have benefited from this form of therapy, and that further controlled studies at the dose of 12 mg/m² were indicated.

Clinical Trials of Mitoxantrone to Support a Multiple Sclerosis Indication

The promising results of the open-label studies of mitoxantrone in MS led Lederle-Europe to conduct two randomized controlled studies in patients with progressive or rapidly deteriorating MS, Studies 901 and 902. The goals of these two studies in the management of patients with MS were different, but both studies demonstrated mitoxantrone efficacy in this disease. The Immunex filing consists of three studies, Studies 901 and 902, and a third study, Study 903, designed to provide long-term safety information on the use of mitoxantrone in MS. Study 903 analyzed retrospectively a large cohort of patients treated with mitoxantrone in a single institution over a 10-year period.

The principal design features and baseline demographic information of the three studies are summarized in the following two tables.

Study Design and Methods in the Immunex Filing

	Study 901	Study 902	Study 903
Trial type	Phase III, multicenter	Phase II, multicenter	Single center
Type of MS	Relapsing progressive* Secondary progressive	Relapsing-relapsing Secondary progressive	Any type of MS
Entry criteria	1-point EDSS increase in 18 months	2-point EDSS increase or 2 relapses in prior 12 months, Gd+ lesions	Any patient given at least one dose of mitoxantrone
Number of groups	3 arms	2 arms	1 arm
Mitoxantrone dose	12 mg/m ² or 5 mg/m ²	20 mg fixed dose†	12 mg/m ² , then adjusted
Control arm	Placebo (methylene blue)	Methylprednisolone	Not applicable
Therapy schedule	Every 3 months	Every month	Every 3 months
Therapy duration	24 months	6 months	Not predefined
Safety evaluations	Every 3 months	Every month	Before each course
Long-term follow-up	1 year after last course	None (on-therapy only)	Variable

Gd+ = gadolinium-enhancing lesions measured by MRI scan; EDSS = expanded disability status scale.

* Defined as patients with relapsing-relapsing MS with residual deficits after relapses.

† Similar to 12 mg/m² in an adult

Characteristics of Patients Treated with Mitoxantrone in Efficacy Cohort

	Study 901	Study 902	Study 903
No. of patients given mitoxantrone	124*	21 [†]	454
Mean age	40 years	31 years	37 years
Gender -- female/male (ratio)	67/57 (1.2)	15/6 (2.5)	276/178 (1.6)
Mean MS duration	9 years	7 years	9 years
Type MS: No. of patients (%)			
Relapsing-remitting/remitting progressive	65 (52%)	17 (81%)	287 (63%)
Secondary progressive	59 (48%)	4 (19%)	102 (22%)
Primary progressive/unknown	0 (0%)	0 (0%)	65 (14%)
Mean EDSS score at baseline	4.5	4.4	5.1
Mean no. of relapses in year prior to entry	1.3	3.1	1.02

* Three additional patients withdrew after one mitoxantrone dose.

[†] One additional patient withdrew after one mitoxantrone dose.

Efficacy Endpoints in Study 901

The objectives of Study 901 were to evaluate the efficacy and safety of two doses of mitoxantrone (5 mg/m² and 12 mg/m²) compared to placebo given over 2 years in patients with active relapsing-progressive or secondary progressive MS. The primary efficacy criterion was a single multivariate statistical test (see Appendix E) comparing mitoxantrone 12 mg/m² to placebo, at the end of Year 2, using five primary efficacy variables evaluated in a predetermined order:

- Change in the Expanded Disability Status Scale (EDSS; see Appendix A).
- Change in the Ambulation Index (AI; see Appendix B).
- Number of relapses requiring corticosteroid treatment during the 2 years of therapy.
- Time to the first relapse requiring corticosteroid treatment.
- Change in the Standard Neurological Status scale (SNS; see Appendix C).

Results for the primary efficacy criterion showed a significant difference in favor of mitoxantrone 12 mg/m² compared to placebo (p < 0.0001). Evaluation of each of the five primary efficacy variables was then conducted individually and showed a statistically significant difference in favor of mitoxantrone 12 mg/m² compared to placebo, as indicated in the table that follows. Since the primary endpoint was a comparison between mitoxantrone 12 mg/m² and placebo, only the p-values for this comparison are provided.

Study 901 – Primary Efficacy Results at Month 24

Endpoint	Placebo N = 64	Mitoxantrone		p-value [‡] (2-sided)
		5 mg/m ² N = 64	12 mg/m ² N = 60	
EDSS change (mean, Month 24 minus baseline) [*]	0.23	-0.23	-0.13	0.0194
AI change (mean, Month 24 minus baseline) [*]	0.77	0.41	0.30	0.0306
SNS change (mean, Month 24 minus baseline) [*]	0.77	-0.38	-1.07	0.0269
No. of treated relapses (total, adjusted for early withdrawals)	76.77	46.88	24.08	0.0002
Time to 1 st relapse requiring treatment (median, months)	14.2	NR	NR	0.0004

NR = median not reached within 24 months.

* Negative values indicate improvement for this scale.

‡ Comparison of mitoxantrone 12 mg/m² vs. placebo.

Mitoxantrone 12 mg/m² was also superior to placebo in all of the secondary clinical endpoints assessing neurological disability, relapses, hospitalizations, and quality of life. A predetermined subset of 110 patients was evaluated by MRI with T1-weighted scans with gadolinium (Gd) enhancement and T-2 weighted scans. The MRI scans with Gd-enhancement showed a significant effect of mitoxantrone on decreasing the development of new enhancing lesions, indicating a beneficial effect on the inflammatory process in the central nervous system (CNS).

Results for mitoxantrone 5 mg/m² were intermediate between placebo and mitoxantrone 12 mg/m² in most efficacy variables, reflecting a dose response effect.

Efficacy Endpoints in Study 902

The primary objective of Study 902 was to evaluate the efficacy of mitoxantrone plus methylprednisolone compared to methylprednisolone alone in patients with MS by assessing the development of central nervous system (CNS) inflammatory brain lesions using MRI scans with Gd-enhancement in patients with highly active MS. Efficacy results at Month 6 are summarized in the following table.

Study 902 - Efficacy Results at Month 6

Endpoint	Mitoxantrone		p-value
	mP (N = 21)	+ mP (N = 21)	
Percent of pts. free of Gd-enhancing lesions on MRIs	31%	90%	0.001
No. of new Gd-enhancing lesions on MRIs (mean)	2.9	0.1	0.001
EDSS change from baseline (mean)	0.1	-1.1	0.013
Annual relapse rate per patient	3.0	0.7	0.003

mP = methylprednisolone.

The percentage of patients free of new Gd-enhancing MRI brain lesions was significantly higher in the mitoxantrone-plus-methylprednisolone group than in the methylprednisolone-alone group from Month 2 to 6 (90% vs. 31%, respectively at Month 6, $p = 0.001$). Other MRI and clinical endpoints related to neurological disability and relapses were also significantly improved in the mitoxantrone-plus-methylprednisolone group compared to the methylprednisolone-alone group.

Summary of Safety

Mitoxantrone was generally well tolerated and had manageable side effects at the doses and schedules used in these studies. Altogether, the three studies provide data on 603 patients with MS treated with mitoxantrone for up to 2 years in the two controlled studies and 10 years in Study 903.

In Study 901, adverse events that were significantly ($p < 0.05$) more frequently reported with mitoxantrone compared to placebo consisted of nausea, alopecia, menstrual disorders, and leukopenia. The intensity of these events was usually mild to moderate. Most events were of short duration and resolved without incident. There were no deaths due to toxicity. Withdrawals due to toxicity were infrequent ($< 5\%$ of patients discontinued due to adverse events). The safety profile of mitoxantrone-plus-methylprednisolone in Study 902 was similar to the data from Study 901. No clinically significant cardiotoxicity was reported in the two randomized trials. The long-term data from Study 903 revealed no toxicities that were not already reported in the two randomized studies.

Conclusions

Two well-designed, randomized studies demonstrated that mitoxantrone administered at a dose of 12 mg/m² by short IV infusion every month for 6 months or every 3 months for 24 months significantly slowed the progression of neurologic impairment, reduced the rate of relapse, and reduced new Gd-enhancing lesions on MRI scan in patients with active MS. The safety profile reported in these trials and the retrospective study show that mitoxantrone had manageable acute side effects, with most adverse events being of mild to moderate intensity and resolving without sequelae.

A decade-long, extensive worldwide experience with mitoxantrone in the treatment of patients with cancer has established its safety profile. Based on the data presented here, Immunex requests FDA approval of a new indication in the management of patients with MS. As a powerful, yet well tolerated, immunosuppressive chemotherapy, mitoxantrone is expected to fulfill an unmet medical need for patients suffering from a serious disease with unsatisfactory therapeutic options.

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Appendix A: Extended Disability Status Scale (EDSS)

Appendix B: Ambulation Index (AI)

Appendix C: Standard Neurological Status (SNS)

Appendix D: Summary of Preclinical Studies in Experimental Allergic
Encephalomyelitis (EAE)

Appendix E: Statistical Methodology for the Primary Efficacy Analysis in Study 901

Appendix F: Summary of Sensitivity Analyses Conducted in Study 901

Appendix G: Published Papers

ABBREVIATIONS AND TERMS

AAN	American Academy of Neurology
AI	Ambulation Index
BL	baseline
CGI	clinical general impression
CI	confidence interval
CNS	central nervous system
CRF	case report form
EAE	experimental allergic encephalomyelitis
ECG	electrocardiogram
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	(Kurtzke) Expanded Disability Status Scale
FDA	Food and Drug Administration
FS	(Kurtzke) Functional Systems
Gamma-GT	gamma glutamyl transpeptidase
Gd	gadolinium
HAQ	Health Assessment Questionnaire
ITT	intent to treat
IV	intravenous
LVEF	left ventricular ejection fraction
MHC	major histocompatibility complex
MITOX	mitoxantrone
mP	methylprednisolone
MRI	magnetic resonance imaging
MS	multiple sclerosis
NCI	National Cancer Institute
NS	not significant
PP	primary progressive
RP	relapsing progressive
RR	relapsing-relapsing
SAE	serious adverse event
SD	standard deviation
SDS	Zung Self-Rating Depression Scale
SEM	standard error of mean
SGOT	serum glutamic oxaloacetic transaminase
SNS	Standard Neurological Status Score
SP	secondary progressive
WBC	white blood cell count
WHO	World Health Organization