

than two years, as long as patients are carefully monitored, and that benefit was maintained.

6.2 Risks of Treatment with Mitoxantrone in MS

Chemotherapy with mitoxantrone was generally well tolerated in the two randomized trials. There were no deaths due to toxicity in either trial. The two studies revealed no toxicities that are not already known from experience with mitoxantrone in patients with cancer. In fact, there were fewer toxicities than those seen in an oncology setting due to the lower dosing regimen.

In Study 901, 10% of patients receiving mitoxantrone at 12 mg/m² discontinued treatment due to an adverse event, and no patient discontinued treatment due to toxicity in the group receiving mitoxantrone at 5 mg/m². There were no treatment discontinuations due to toxicity in Study 902.

The most common acute adverse events associated with mitoxantrone in MS therapy include nausea, alopecia, urinary tract infection, menstrual disorders, stomatitis, and leukopenia. Adverse event intensity was usually mild to moderate.

- Nausea is temporally associated with mitoxantrone administration and resolves in 1-2 days. It can be prevented with appropriate therapy. As expected, leukopenia generally occurred 7 to 14 days after mitoxantrone administration and lasted about 1 week.
- Fever associated with neutropenia was rarely reported at the doses and schedules used in the two randomized trials. If fever occurs, it is temporally associated with leukopenia nadir. Fever is not a direct side effect of mitoxantrone as reported with the interferons.
- Alopecia, when present, was usually mild and reversible after discontinuation of mitoxantrone therapy.

- Menstrual disorders could be attenuated with the use of appropriate hormonal manipulation such as birth control pills, and most reversed after completion of mitoxantrone therapy. Because of the potential risk of teratogenicity, women should adopt strict contraceptive methods while receiving mitoxantrone.

6.2.1 Mitoxantrone Use in Cancer Patients

Mitoxantrone has been studied extensively in clinical trials in oncology and has been commercially available for over 10 years in the U.S. and worldwide. For example, approximately 15,000 cancer patients were treated with mitoxantrone in the U.S. in 1998 alone (over 80,000 vials sold). Mitoxantrone doses and schedules usually ranged between 8 and 14 mg/m² repeated every 3-4 weeks. In bone marrow transplantation and leukemia, single doses between 30 and 80 mg/m² have been administered. The safety profile of mitoxantrone in cancer patients is well characterized. The most frequent adverse events associated with mitoxantrone treatment in cancer patients are transient nausea, emesis, anorexia, fatigue, alopecia, and marrow suppression.

6.2.2 Cardiac Effects of Mitoxantrone

Mitoxantrone belongs to a class of agents associated with cardiac toxicity related to cumulative dose. Mitoxantrone-associated cardiotoxicity is characterized by electrocardiographic changes, decreased LVEF, and development of congestive heart failure. In a retrospective database analyses, the risk of symptomatic congestive heart failure was estimated to be 2.6% of patients receiving mitoxantrone at a cumulative dose of 140 mg/m². Cardiotoxicity occurs while on mitoxantrone therapy or within 1 year of discontinuing treatment. Cardiotoxicity seldom, if ever, occurs more than 1 year after discontinuing therapy. The following risk factors have been established for mitoxantrone-associated cardiotoxicity in patients treated with mitoxantrone alone or in combination with other antineoplastic agents: prior anthracycline therapy, pre-existing cardiovascular diseases, prior mediastinal radiotherapy, and total cumulative mitoxantrone dose (Gams 1984, Dukart 1984).

No major cardiac toxicity was reported in Study 901. An LVEF $\leq 50\%$ was reported in three patients treated with mitoxantrone at 12 mg/m², two patients treated with mitoxantrone at 5 mg/m², and one patient receiving placebo. There was no cardiac toxicity reported by clinical, radiological, or echocardiographic evaluation in Study 902. Mitoxantrone was given at doses up to 96 mg/m² in the two randomized studies; thus, it is difficult to predict what would be the cardiac effects of mitoxantrone if it were given beyond this dose in patients with MS. However, there are no data to suggest that the cardiac effects of mitoxantrone in patients with MS will be different than the effects seen in patients with cancer.

Cardiac monitoring while receiving mitoxantrone therapy should be useful to identify patients with potential cardiac toxicity. Based on the results from the three studies in MS presented in this filing, and the large oncology experience, an LVEF assessment is recommended when a patient reaches a cumulative dose of 100 mg/m². If mitoxantrone is continued beyond that dose, it is recommended that LVEF assessment be repeated after every course of therapy for up to a cumulative dose of 140 mg/m² in the presence of decreased LVEF by $\geq 10\%$ from baseline or $< 50\%$. The increased risk of chronic heart failure should be considered when mitoxantrone therapy is continued beyond a cumulative dose of 140 mg/m².

6.2.3 Long-Term Treatment with Mitoxantrone in Patients with MS

Study 903, a study that retrospectively analyzed 454 patients with MS who had received mitoxantrone for up to 10 years, showed no unexpected toxicity associated with the long-term use of mitoxantrone. In particular, there was no evidence of delayed cardiotoxicity, secondary leukemia, or myelodysplastic syndromes after mitoxantrone discontinuation. This study showed that it is possible to treat safely MS patients with mitoxantrone when using careful monitoring.