

filing demonstrates that mitoxantrone fulfills an unmet medical need for patients who lack satisfactory therapy for this debilitating disease.

## **2.0 Mitoxantrone**

Mitoxantrone is an anthracenedione agent with a molecular weight of 454 daltons that has antiproliferative and immunosuppressive activity. In the U.S., mitoxantrone was first approved in 1987 for the treatment of adult patients with acute nonlymphocytic leukemia. In this disease, it is given at a dose of 12 mg/m<sup>2</sup> per day for 3 days, with courses repeated every 3 to 6 weeks. In 1996, mitoxantrone was also approved to reduce cancer-related pain in patients with symptomatic hormone-refractory prostate cancer. In this disease, it is given at a dose of 12-14 mg/m<sup>2</sup> once every 3 weeks. Mitoxantrone has also been used at single doses as high as 80 mg/m<sup>2</sup> in patients with acute leukemia and in patients undergoing myeloablative therapy before bone marrow transplantation.

Mitoxantrone has a dual effect on nucleic acids: it induces DNA strand crosslinks and strand breaks. It also inhibits topoisomerase II, an enzyme necessary for DNA uncoiling and repair. Mitoxantrone has antiproliferative effects both on dividing and nondividing cells.

Mitoxantrone pharmacokinetics have been well characterized in patients with cancer. Mitoxantrone has a triphasic plasma elimination profile, with a terminal half-life of up to 72 hours. Mitoxantrone has long residence time in tissues, e.g., up to 14 days in leukocytes.

The activity of mitoxantrone in MS is considered to be due to its antiproliferative effects on the immune system, including suppression of B cells, CD4 helper cells, and macrophages. Mitoxantrone also induces immunomodulatory effects by reducing antigen presentation by macrophages, decreasing production of cytokines such as IL-2 and TNF $\alpha$  produced by these cells, and increasing the activity of CD8 suppressor cells.

In vitro experiments and rodent models of experimental allergic encephalomyelitis (EAE) have indicated that mitoxantrone may have a role in the management of autoimmune diseases of the CNS. A summary of these experiments is presented in Appendix D. In