CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-120

FINAL PRINTED LABELING

October 13, 2000

Package Insert

NOVANTRONE®

mitoxantrone

for injection concentrate

WARNING

NOVANTRONE® (mitoxantrone for injection concentrate) should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy agents.

NOVANTRONE should be given slowly into a freely flowing intravenous infusion. It must *never* be given subcutaneously, intramuscularly, or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration. (See **ADVERSE REACTIONS, General,** Cutaneous)

NOT FOR INTRATHECAL USE. Severe injury with permanent sequelae can result from intrathecal administration. (See **WARNINGS, General**)

Except for the treatment of acute nonlymphocytic leukemia, NOVANTRONE therapy generally should not be given to patients with baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving NOVANTRONE.

Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with NOVANTRONE or months to years after termination of therapy. Use of NOVANTRONE has been associated with cardiotoxicity; this risk increases with cumulative dose. In cancer patients, the risk of symptomatic congestive heart failure (CHF) was estimated to be

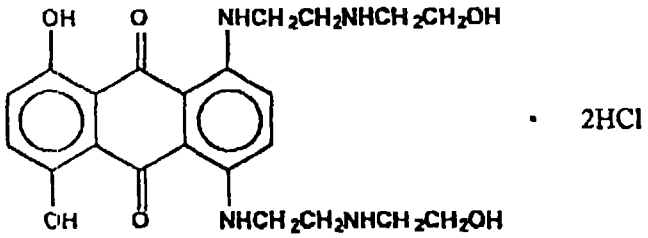
2.6% for patients receiving up to a cumulative dose of 140 mg/m^2. For this reason, patients should be monitored for evidence of cardiac toxicity and questioned about symptoms of heart failure prior to initiation of treatment. Patients with multiple sclerosis who reach a cumulative dose of 100 mg/m^2 should be monitored for evidence of cardiac toxicity prior to each subsequent dose. Ordinarily, patients with multiple sclerosis should not receive a cumulative dose greater than 140 mg/m^2. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with NOVANTRONE may occur at lower cumulative doses whether or not cardiac risk factors are present. For additional information, see **WARNINGS, Cardiac Effects**, and **DOSAGE AND ADMINISTRATION.**

Secondary acute myelogenous leukemia (AML) has been reported in cancer patients treated with anthracyclines. NOVANTRONE is an anthracenedione, a related drug. The occurrence of refractory secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Secondary leukemias have been reported in cancer patients treated with NOVANTRONE in combination with other cytotoxic agents; the incidence of these events has not been quantified.

DESCRIPTION

NOVANTRONE (mitoxantrone hydrochloride) is a synthetic antineoplastic anthracenedione for intravenous use. The molecular formula is $C_{22}H_{28}N_4O_6 \cdot 2HCl$ and the molecular weight is 517.41. It is supplied as a concentrate that MUST BE DILUTED PRIOR TO INJECTION. The concentrate is a sterile, nonpyrogenic, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and acetic acid (0.046% w/v) as inactive ingredients. The solution has a pH of 3.0 to 4.5 and contains

0.14 mEq of sodium per mL. The product does not contain preservatives. The chemical name is 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl) amino]ethyl]amino]-9,10-anthracenedione dihydrochloride and the structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Mitoxantrone, a DNA-reactive agent that intercalates into deoxyribonucleic acid (DNA) through hydrogen bonding, causes crosslinks and strand breaks. Mitoxantrone also interferes with ribonucleic acid (RNA) and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytocidal effect on both proliferating and nonproliferating cultured human cells, suggesting lack of cell cycle phase specificity.

NOVANTRONE has been shown in vitro to inhibit B cell, T cell, and macrophage proliferation and impair antigen presentation, as well as the secretion of interferon gamma, TNFα, and IL-2.[1-4]

Pharmacokinetics

Pharmacokinetics of mitoxantrone in patients following a single intravenous administration of NOVANTRONE can be characterized by a three-compartment model. The mean alpha half-life of mitoxantrone is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours and the mean gamma (terminal or elimination) half-life is 23 to 215 hours

(median approximately 75 hours). Pharmacokinetic studies have not been performed in humans receiving multiple daily dosing. Distribution to tissues is extensive: steady-state volume of distribution exceeds 1000 L/m^2. Tissue concentrations of mitoxantrone appear to exceed those in the blood during the terminal elimination phase. In the healthy monkey, distribution to brain, spinal cord, eye, and spinal fluid is low.

In patients administered 15-90 mg/m^2 of NOVANTRONE intravenously, there is a linear relationship between dose and the area under the concentration-time curve (AUC).

Mitoxantrone is 78% bound to plasma proteins in the observed concentration range of 26-455 ng/mL. This binding is independent of concentration and is not affected by the presence of phenytoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin, or aspirin.

Metabolism and Elimination

Mitoxantrone is excreted in urine and feces as either unchanged drug or as inactive metabolites. In human studies, 11% and 25% of the dose were recovered in urine and feces, respectively, as either parent drug or metabolite during the 5-day period following drug administration. Of the material recovered in urine, 65% was unchanged drug. The remaining 35% was composed of monocarboxylic and dicarboxylic acid derivatives and their glucuronide conjugates. The pathways leading to the metabolism of NOVANTRONE have not been elucidated.

In vitro drug interaction studies have demonstrated that mitoxantrone did not inhibit CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 across a broad concentration range. The results of in vitro induction studies are inconclusive, but suggest that mitoxantrone is a weak inducer of CYP450 2E1 activity.

Special Populations

Gender: The effect of gender on mitoxantrone pharmacokinetics is unknown.

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