

DTIC-Dome®

(dacarbazine)

08844898, R.0

Sterile

11778

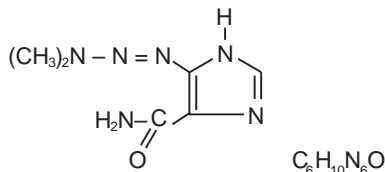
WARNING

It is recommended that DTIC-Dome (dacarbazine) be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

1. Hemopoietic depression is the most common toxicity with DTIC-Dome (See Warnings).
2. Hepatic necrosis has been reported (See Warnings).
3. Studies have demonstrated this agent to have a carcinogenic and teratogenic effect when used in animals.
4. In treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit against the risk of toxicity.

DESCRIPTION

DTIC-Dome Sterile (dacarbazine) is a colorless to an ivory colored solid which is light sensitive. Each vial contains 100 mg of dacarbazine, or 200 mg of dacarbazine (the active ingredient), anhydrous citric acid and mannitol. DTIC-Dome is reconstituted and administered intravenously (pH 3–4). DTIC-Dome is an anticancer agent. Chemically, DTIC-Dome is 5-(3, 3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) with the following structural formula:



CLINICAL PHARMACOLOGY

After intravenous administration of DTIC-Dome, the volume of distribution exceeds total body water content suggesting localization in some body tissue, probably the liver. Its disappearance from the plasma is biphasic with initial half-life of 19 minutes and a terminal half-life of 5 hours.¹ In a patient with renal and hepatic dysfunctions, the half-lives were lengthened to 55 minutes and 7.2 hours.¹ The average cumulative excretion of unchanged DTIC in the urine is 40% of the injected dose in 6 hours.¹ DTIC is subject to renal tubular secretion rather than glomerular filtration. At therapeutic concentrations DTIC is not appreciably bound to human plasma protein.

In man, DTIC is extensively degraded. Besides unchanged DTIC, 5-aminoimidazole -4 carboxamide (AIC) is a major metabolite of DTIC excreted in the urine. AIC is not derived endogenously but from the injected DTIC, because the administration of radioactive DTIC labeled with ¹⁴C in the imidazole portion of the molecule (DTIC-2-¹⁴C) gives rise to AIC-2-¹⁴C¹.

Although the exact mechanism of action of DTIC-Dome is not known, three hypotheses have been offered:

1. inhibition of DNA synthesis by acting as a purine analog
2. action as an alkylating agent
3. interaction with SH groups

INDICATIONS AND USAGE

DTIC-Dome is indicated in the treatment of metastatic malignant melanoma. In addition, DTIC-Dome is also indicated for Hodgkin's disease as a second-line therapy when used in combination with other effective agents.

CONTRAINDICATIONS

DTIC-Dome is contraindicated in patients who have demonstrated a hypersensitivity to it in the past.

WARNINGS

Hemopoietic depression is the most common toxicity with DTIC-Dome and involves primarily the leukocytes and platelets, although, anemia may sometimes occur. Leukopenia and thrombocytopenia may be severe enough to cause death. The possible bone marrow depression requires careful monitoring of white blood cells, red blood cells, and platelet levels. Hemopoietic toxicity may warrant temporary suspension or cessation of therapy with DTIC-Dome.

Hepatic toxicity accompanied by hepatic vein thrombosis and hepatocellular necrosis resulting in death, has been reported. The incidence of such reactions has been low; approximately 0.01% of patients treated. This toxicity has been observed mostly when DTIC-Dome has been administered concomitantly with other anti-neoplastic drugs; however, it has also been reported in some patients treated with DTIC-Dome alone.

Anaphylaxis can occur following the administration of DTIC-Dome.

PRECAUTIONS

Hospitalization is not always necessary but adequate laboratory study capability must be available. Extravasation of the drug subcutaneously during intravenous administration may result in tissue damage and severe pain. Local pain, burning sensation, and irritation at the site of injection may be relieved by locally applied hot packs.

Carcinogenicity of DTIC was studied in rats and mice. Proliferative endocardial lesions, including fibrosarcomas and sarcomas were induced by DTIC in rats. In mice, administration of DTIC resulted in the induction of angiosarcomas of the spleen.

Pregnancy Category C. DTIC-Dome has been shown to be teratogenic in rats when given in doses 20 times the human daily dose on day 12 of gestation. DTIC when administered in 10 times the human daily dose to male rats (twice weekly for 9 weeks) did not affect the male libido, although female rats mated to male rats had higher incidence of resorptions than controls. In rabbits, DTIC daily dose 7 times the human daily dose given on Days 6–15 of gestation resulted in fetal skeletal anomalies. There are no adequate and well controlled studies in pregnant women. DTIC-Dome should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for DTIC-Dome in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

Symptoms of anorexia, nausea, and vomiting are the most frequently noted of all toxic reactions. Over 90% of patients are affected with the initial few doses. The vomiting lasts 1–12 hours and is incompletely and unpredictably palliated with phenobarbital and/or prochlorperazine. Rarely, intractable nausea and vomiting have necessitated discontinuance of therapy with DTIC-Dome. Rarely, DTIC-Dome has caused diarrhea. Some helpful suggestions include restricting the patient's oral intake of food for 4–6 hours prior to treatment. The rapid toleration of these symptoms suggests that a central nervous system mechanism may be involved, and usually these symptoms subside after the first 1 or 2 days.

There are a number of minor toxicities that are infrequently noted. Patients have experienced an influenza-like syndrome of fever to 39°C, myalgias and malaise. These symptoms occur usually after large single doses, may last for several days, and they may occur with successive treatments.

Alopecia has been noted as has facial flushing and facial paresthesia. There have been few reports of significant liver or renal function test abnormalities in man. However, these abnormalities have been observed more frequently in animal studies.

Erythematous and urticarial rashes have been observed infrequently after administration of DTIC-Dome. Rarely, photosensitivity reactions may occur.

OVERDOSAGE

Give supportive treatment and monitor blood cell counts.

DOSAGE AND ADMINISTRATION

Malignant Melanoma: The recommended dosage is 2 to 4.5mg/kg/day for 10 days. Treatment may be repeated at 4 week intervals.²

An alternate recommended dosage is 250mg/square meter body surface/day I.V. for 5 days. Treatment may be repeated every 3 weeks.^{3,4}

Hodgkin's Disease: The recommended dosage of DTIC-Dome in the treatment of Hodgkin's disease is 150mg/square meter body surface/day for 5 days, in combination with other effective drugs. Treatment may be repeated every 4 weeks.⁵ An alternative recommended dosage is 375mg/square meter body surface on day 1, in combination with other effective drugs, to be repeated every 15 days.⁶

DTIC-Dome (dacarbazine) 100mg/vial and 200mg/vial are reconstituted with 9.9 mL and 19.7 mL, respectively, of Sterile Water for Injection, U.S.P. The resulting solution contains 10mg/mL of dacarbazine having a pH of 3.0 to 4.0. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously.

The reconstituted solution may be further diluted with 5% dextrose injection, U.S.P. or sodium chloride injection, U.S.P. and administered as an intravenous infusion.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection, U.S.P. or sodium chloride injection, U.S.P., the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.⁷⁻¹² There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

20 mL vials containing 200 mg of DTIC-Dome as sterile dacarbazine in boxes of 12. Store in a refrigerator 2°C to 8°C (36°F to 46°F).

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