Dacarbazine for Injection, USP

It is recommended that Dacarbazine for Injection be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

1. Hematopoietic depression is the most common toxicity with Dacarbazine for Injection (see WARNINGS).
2. Hepatic necrosis has been reported (see WARNINGS).
3. Cardiac and tracheal effects 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

Dacarbazine for Injection is a colorless to an ivory colored solid which is light sensitive. Each vial contains 200 mg of dacarbazine (the active ingredient), citric acid monohydrate and mannitol. Dacarbazine for Injection is reconstituted and administered intravenously (pH 3–4). Dacarbazine is an anticancer agent designated chemically as 5-(3,5-dimethyl-4-furfuryl)-2-carboxamide in the following structural formula:

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(C_8H_7N_2O_2)_2N_2 = \text{N} + \text{N}
\]

\[
HNC
\]

\[
\text{CaH}_{24}\text{NaO}_4
\]

CLINICAL PHARMACOLOGY

After intravenous administration of Dacarbazine for Injection, the volume of distribution exceeds total body water content suggesting localization in some body tissues. 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. In a patient with renal and hepatic dysfunctions, the half-lives were lengthened to 55 minutes and 7.2 hours. The average cumulative excretion of dacarbazine was 10% with a biphasic with initial half-life of 19 minutes and a terminal half-life of 5 hours. Dacarbazine is subject to renal tubular secretion rather than glomerular filtration. All therapeutic concentrations dacarbazine is not appreciably bound to human plasma protein.

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

Although the exact mechanism of action of Dacarbazine for Injection is not known, three hypotheses have been offered:
1. inhibition of DNA synthesis by acting as a purine analog
2. acts as an alkylating agent
3. interaction with 5m groups

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Dacarbazine for Injection is contraindicated in patients who have demonstrated a hypersensitivity to it in the past.

WARNINGS

Hematopoietic depression is the most common toxicity with Dacarbazine for Injection 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. Hematopoietic toxicity may warrant temporary suspension or cessation of therapy with Dacarbazine for Injection.

Hepatic toxicity accompanied by hepatic vein thrombosis and hepatic cirrhosis resulting in death, has been reported. The incidence of such reactions has been low; approximately 0.01% of patients treated. There have been few reports of significant hepatic toxicity in the clinical trials with dacarbazine. Hepatic toxicity has been observed mostly when Dacarbazine for Injection has been administered concomitantly with other antineoplastic drugs; however, it has also been reported in some patients treated with Dacarbazine for Injection alone. Anaplasy may occur following the administration of Dacarbazine for Injection.

PRECAUTIONS

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

Chemotherapy of dacarbazine was studied in rats and mice. Protrusive endocardial lesions, including fibrosis in and sercosas were induced by dacarbazine in rats. In mice, administration of dacarbazine resulted in the induction of angiosarcomas of the spleen.

USAGE IN PREGNANCY

Pregnancy Category C: Dacarbazine for Injection has been shown to be teratogenic in rats when given in doses, 20 times the human daily dose on day 12 of gestation. Dacarbazine when administered to 10 times the human daily dose to male rats (four weeks on 9 days) did not affect the male rats, although female rats male to male rats had higher incidence of resorptions than controls. In rabbits, rabbits daily dose 7 times the human daily dose given on days 6 - 15 of gestation resulted in fetal skeletal anomalies. There were no adverse and well controlled studies in pregnant women. Dacarbazine for Injection 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 Dacarbazine for Injection in animals, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance to 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 parallel with gastrointestinal and/or proctitis. Rarely, intractable nausea and vomiting have necessitated discontinuance of therapy with Dacarbazine for Injection. Rarely, Dacarbazine for Injection has caused diarrhea. Some helpful suggestions include restricting the patient’s oral intake of food for 4 – 6 hours prior to treatment. The rapid onset 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 50°C, myalgia and malaise. These symptoms occur usually after large single doses, may last for several days, and 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 Dacarbazine for Injection. Rarely, photosensitivity reactions may occur.

OVERDOSAGE

Provide supportive treatment and monitor blood cell counts.

DOSAGE AND ADMINISTRATION

Maligant Malignancies: The recommended dosage is 2 to 4 mg/kg/day for 10 days. Treatment may be repeated at 4 week intervals. An alternative recommended dosage is 350 mg/m² body surface area/day for 5 days. Treatment may be repeated every 3 weeks.

Hodgkin’s Disease: The recommended dosage of Dacarbazine for Injection in the treatment of Hodgkin’s disease is 150 mg/m² body surface area for 5 days, in combination with other effective drugs. Treatment may be repeated every 4 weeks. An alternative recommended dosage is 175 mg/m² body surface area on day 1, in combination with other effective drugs. To be repeated every 4 weeks.

Dosage is usually given in a single intravenous injection. The resulting solution contains 10 mg/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 can be further diluted with 5% dextrose injection, USP or sodium chloride injection, USP. The resulting solution may be further diluted with 5% dextrose injection, USP or sodium chloride injection, USP, the resulting solution may be stored at 4°C for up to 2 hours or at normal room conditions for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection, USP or sodium chloride injection, USP, 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 published1-7. There is no agreement that all the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

MDC 61703-322-22, 200 mg of Dacarbazine for Injection per vial as sterile dacarbazine packaged in individual cartons.

Storage Conditions

Store in a refrigerator 2°C to 8°C (36°F to 46°F).

REFERENCES


Manufactured for:
Fausting Pharmaceutical Co.
3 Mayne Group Complex
Paracelsus, NJ 07652
By: Mayne Pharma Pty Ltd
Mungrave VIC 3170
Australie

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