DTI for Injection

Dacarbazine 100mg, 200mg

COMPOSITION
Each vial contains

Dacarbazine ..... 100 mg

Dacarbazine ..... 200 mg

DESCRIPTION
White to pale yellow, freeze-dried powder in an amber vial.

Dacarbazine is a structural analogue of 5-amino-imidazole-4-carboxamide which is an intermediate in purine biosynthesis.

ACTIONS
Cytotoxic agent.

PHARMACOLOGY
Site and mode of action: This drug inhibits cell replication by an unknown mechanism. However, three possible mechanisms have been postulated:
Since dacarbazine is an analogue of 5-amino-imidazole-4-carboxamide, an intermediate in the de novo biosynthesis of purine, it might interfere with purine biosynthesis and hence DNA bio-synthesis. This appears to be true at high concentrations of the drug, but low concentrations appear to enhance DNA, RNA and protein biosynthesis.
One metabolite of dacarbazine, diazomethane, is an alkylating agent and may act in the same way as the nitrogen mustards.
The drug might act as a sulphydryl reagent since the inhibition of bacterial growth by dacarbazine can be prevented by glutathione.

PHARMACOKINETICS
Absorption : Dacarbazine is poorly absorbed from the GI tract. Peak plasma concentrations of about 8 μg/mL are reached immediately following administration of dacarbazine 4.5 mg/kg
by IV push.

Distribution : The volume of distribution of dacarbazine exceeds total body water content, suggesting localization in some body tissue, probably the liver. The drug is only slightly bound to plasma proteins. Dacarbazine crosses the blood-brain barrier to a limited extent; CSF concentrations are reported to be about 14 % of plasma concentrations. It is not known if dacarbazine crosses the placenta or distributes into milk.

Elimination : Plasma concentrations of dacarbazine appear to decline in a biphasic manner. In individuals with normal renal function, the half-life in the initial phase ($t_{1/2\alpha}$) averages 19 minutes and the half-life in the terminal phase ($t_{frac12;\beta}$) averages 5 hours. The manufacturer states that in one patient with renal and hepatic dysfunction, the $t_{1/2\,\alpha}$ was 55 minutes and the $t_{1/2\beta}$ was 7.2 hours.

Dacarbazine is extensively metabolized. Dacarbazien is N-demethylated by liver microsomal enzymes to 5-(3 -monomethyl-1)-1H-imidazole -4-carboxamide(MIC) which spontaneously decomposes to form AIC plus an unidentified alkylating or methylating moiety. Small amounts of the drug may also be converted to the diazonium salt of AIC(Ciazo-ICA), which undergoes spontaneous intramolecular coupling to form 2-azahypoxanthine. Some dacarbazine metabolites may contribute to the antineoplastic efect of the drug. Metabolism of dacarbazine may be enhanced bu agents such as phenobarbital and phenytoin which induce liver microsomalenzymes.
Dacarbazine is excreted in the urine by tubular secretion; 30 -46% of an administered dose is excreted in the urine within 6 hours. About half of the drug excreted is recovered as unchanged dacarbazine and half as AIC.

INDICATIONS
Treatment of metastatic malignant melanoma and various sarcomas both alone and in combination with other agents.
Note : The use of dacarbazine is restricted to hospitals with an oncology service.

ADVERSE EFFECTS
More Common Reactions: Gastrointestinal: 90% of patients experience the following effects in the first 2 days of treatment but after this, a degree of tolerance may develop: Nausea, vomiting, diarrhoea (tolerance to these effects may develop after about 2 days of treatment). Vomiting lasts 1 -12 hrs and is incompletely and unpredictably palliated with phenobarbitone and/or prochlorperazine. Rarely, intractable nausea and vomiting have necessitated discontinuance of dacarbazine therapy.

Haematological: Bone marrow depression (25%). (See Life-Threatening Reactions as follows.) Leucocytopenia was usually seen 14 days after commencement of therapy but was noted as early as day 10 and, in 10% of patients, as late as day 30 (ie, 25 days after completion of therapy). The average length of duration was I week and the longest, 3 weeks. Thrombocytopenia was most frequently seen 18 days after commencement of therapy but in 43% of patients, it was noted by day 12 and in 10%, not until after day 30. The average length of duration was 1 week and the longest, 3 weeks.
Less Common Reactions: Cardiovascular: Facial flushing.

Dermatological (1%, usually transient) : Rash, alopecia. General (3%): Flu-like symptoms with fever to 39°C, severe myalgias and malaise. This syndrome usually occurs after large single doses approximately 7 days after treatment with dacarbazine and lasts 7-21 days. It may recur with successive treatments.

Hepatic (5%, usually transient): Increases in transaminases (AST and ALT), alkaline phosphatase, LDH. Levels usually return to normal within 2 weeks; hepatic toxicity accompanied by hepatic vein thrombosis and hepatocellular necrosis (Budd-Chiari Syndrome) resulting in death (see Warnings) (0.01%).

Nervous System (3%, usually transient): Blurred vision, seizures, headache, paraesthesia, confusion, malaise, lethargy.

Life-Threatening Reactions: Death due to agranulocytosis or thrombocytopenia occurred in about 0.4% patients in clinical trials; Budd-Chiari Syndrome (see Warnings).

PRECAUTIONS
Toxicity: In the treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit against the risk of toxicity (see Warnings and Adverse Reactions).
DTI should be administered preferably to patients who are hospitalized and who can be observed carefully and frequently during and after therapy.
Restriction of food intake for 4-6 hours prior to treatment may reduce the severity of nausea and vomiting which occurs in most patients particularly during the first 2 days of treatment. Administration of an antiemetic may also reduce the severity of those effects. Impairment of Lever and Renal Function: See Impaired Hepatic and Renal Function under Dosage & Administration. Avoid contact with the skin and eyes.

WARNINGS
Haematopoietic depression is the most common toxicity with dacarbazine and involves primarily the leukocytes and megakaryocytes causing depression of platelets, but also other blood-forming elements.
Leukopenia and thrombocypenia 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. Haematotoxicity may warrant temporary suspension or cessation of therapy with dacarbazine.
Hepatic toxicity accompanied by hepatic vain thrombosis and hepatocellular necrosis resulting in death has been reported. The incidence of such reaction has been low, approximately 0.01% of patients treated. This toxicity has been observed mostly when dacarbazine has been administered concomitantly with other antineoplastic drugs; however, it has also been reported in some patients treated with dacarbazine alone. Anaphylaxis can occur following the administration of dacarbazine.

CONTRAINDICATIONS
Patients with known hypersensitivity to DTI (Dacarbazine). Patients who have previously had severe myelosuppression.

USE IN PREGNANCY AND LACTATION
1. Studies have demonstrated that this agent is teratogenic when administered to animals. Dacarbazine therefore should not be administered to pregnant women or women who are suspected of pregnancy.
2. Since the safety use in nursing mothers has not been established, breast-feeding should be avoided under dacarbazine therapy.

USE IN CHILDREN
Safe use in children has not been established.

DRUG INTERACTION
Microsomal liver enzyme inducer, eg barbiturates, rifampicin, phenytoin may theoretically hasten the activation of dacarbazine to AIC (aminoimidazole-carboxamide).
Mercaptopurin, Azathioprine, Allopurinol: Dacarbazine inhibits xanthine oxidase and may theoretically potentiate the activity of these drugs.

DOSAGE & ADMINISTRATION
Reconstitution and Administration
Dacarbazine is administered by IV injection or infusion. Care should be taken to avoid extravasation of the drug. The powder for injection is reconstituted by adding 9.9mL /19.7 mL of sterile water for injection to a vial labeled as containing 100mg /200mg of the drug. The resultant solution contains 10 mg of dacarbazine per mL. Reconstituted solutions may be administered by IV push over a 1 minute period. Alternatively, the reconstituted solution may be further diluted with up to 250 mL of 5 % dextrose or 0.9 % sodium chloride injection and infused IV over a 15-30 minute period.

Dosage
Dosage of dacarbazine must be based on the clinical and hematologic response and tolerance of the patient in order to obtain optimum therapeutic results with minimum adverse effects. Clinicians should consult published protocols for the dosage of dacarbazine and other chemotherapeutic agents and the method and sequence of administration.

1. Malignant Melanoma: For the treatment of metastatic melanoma, the usual adult dosage of dacarbazine is 2 - 4.5 mg/kg daily for 10 days. It appears that the drug may be equally efficacious at the lower dosage. This regimen may be repeated each 4 weeks intervals. Alternatively, 250 mg/m^2 may be given daily for 5 days. This treatment course may be repeated every 3 weeks.

2. Children: No special information was submitted to indicate whether or not children require a different dosage range or whether they metabolise the drug differently or react differently to the drug.

Geriatric: As for pediatric use.

3. Impaired Hepatic Function: As the drug partly undergoes metabolism in the liver, impairment of liver function is likely to necessitate a variation in dosage (see Pharmacokinetics under Actions).

4. Impaired Renal Function: As the drug is excreted 50% unchanged in the urine by tubular secretion, impairment of renal function is likely to necessitate a variation in dosage (see Pharmacokinetics under Actions).

5. Other: Combination with other antineoplastic agents.
Dosage of dacarbazine must be based on the clinical and hematologic response and tolerance of the patient in order to obtain optimum therapeutic results. Combinations of cancer chemotherapeutic agents have often shown an improved response over the use of single agents. This has not been the case in metastatic malignant melanoma except at a very high and toxic dosage of the combinations in small numbers of patients. However, treatment of various soft tissue sarcomata combinations with doxorubicin and/or vincristine have increased the remission rates. The user should be familiar with the current cancer chemotherapeutic literature.

SYMTOMS AND TREATMENT FOR OVERDOSAGE
Signs and symptoms
Severe bone marrow depression and gastrointestinal effects such as nausea, vomiting and diarrhea may be expected.

Treatment
Cease dacarbazine administration and institute supportive measures e.g. appropriate transfusions for bone marrow depression. (See Haematological under Adverse Reactions).

PRODUCT SHELF LIFE
3 years from the date of manufactured.

STORAGE
Preserve in sealed containers. Store in a refrigerator, protected from light at the temperature between 2°C-8°C.
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, the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

PACKAGE
100 mg/ Vial or 200 mg / Vial packed in a box of 1 vial and 10 vials in an outer box.

Revised : June 2006

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3410200010-70808MYS