DBL™ DACARBAZINE FOR INJECTION
(Dacarbazine)

1. NAME OF THE MEDICINE

Dacarbazine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted as directed each mL of the solution in the 200 milligram vial contains dacarbazine 10 milligrams, citric acid monohydrate 10 milligrams and mannitol 3.75 milligrams.

For the full list of excipients, see Section 6.1 **List of excipients**.

3. PHARMACEUTICAL FORM

Dacarbazine is a colourless to pale yellow solid, sensitive to light. It is slightly soluble in water and alcohol. DBL™ Dacarbazine for Injection is a sterile parenteral dosage form for reconstitution. The pH of the reconstituted solution is 3.0 - 4.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Chemotherapy of metastatic malignant melanoma and various sarcomas. In other cancers, the available evidence shows dacarbazine to be ineffective or less effective than established regimens.

Note: The use of dacarbazine is restricted to hospitals with an oncology service.

4.2 Dose and Method of Administration

Dosage
Adult
There are two commonly used dose regimens:

1. 4.5 milligrams/kg/day for 10 days; the 10 day course may be repeated every 4 weeks.

   Note: 2 milligrams/kg/day for 10 days has been used by one investigator and found to be equally as effective as the higher dose.

2. 250 milligrams/m^2/day for 5 days; the 5 day course may be repeated every 3 weeks.

In general, effectiveness is likely to be evident after the second course of dacarbazine. Of the 1427 patients with metastatic malignant melanoma treated with dacarbazine, 81 patients (5.7%) had complete remissions and 208 patients (14.6%) had partial remissions with a total response rate of 20.3%. The duration of remissions (partial and

complete combined) varied from 5 to 100 weeks. The median remission duration obtained by three principle investigators was about 6 months. Once a patient has relapsed it is unlikely that subsequent courses of dacarbazine will be effective.

Paediatric
No special information 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 paediatric use.

Combination therapy
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, in 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.

Method of administration
Administration is by the intravenous route only.

Reconstitute vial contents by adding 19.7 mL of Water for Injections to the 200 milligrams vial.

The resulting solution is hypotonic and will contain 10 milligrams/mL of dacarbazine with a pH of 3 to 4.

Intravenous injection may be given over about one minute. Extravasation of the drug into surrounding tissue during intravenous administration may result in tissue damage and severe pain.

Intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

Dosage adjustments
With 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 Section 5.2 **Pharmacokinetic Properties**).

With 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 Section 5.2 **Pharmacokinetic Properties**).

Handling precautions

As with all antineoplastic agents, trained personnel should prepare DBL™ Dacarbazine for Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling dacarbazine. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed, thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as dacarbazine.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare DBL™ Dacarbazine for Injection, or articles associated with body waste should be disposed off by placing in a double sealed polythene bag and incinerated at 1100°C.

4.3 Contraindications

- Patients who are pregnant or are breast feeding.
- Patients with known hypersensitivity to the drug.
- Patients who have previously had severe myelosuppression.

4.4 Special Warnings and Precautions for Use

Haematopoietic depression is the most serious form of toxicity and involves primarily the leucocytes and megakaryocytes causing depression of platelets, but also other blood forming elements. Leucopenia and thrombocytopenia may be severe enough to cause death. Careful monitoring of red and white blood cells and platelets is required. Haematotoxicity may warrant temporary suspension or termination of therapy.

Hepatic toxicity accompanied by hepatic vein thrombosis and hepatocellular necrosis (Budd-Chiari Syndrome) 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 when dacarbazine has been administered concomitantly with other antineoplastic drugs; however, it has also been reported in some patients treated with dacarbazine alone.

Toxicity: In the treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit against the risk of toxicity (see above and Section 4.8 **Adverse Effects (Undesirable Effects)**).

Administer only to patients in hospitals with an oncology service so that they can be observed carefully and frequently during and after therapy particularly for haematopoietic toxicity.

Restriction of food intake for 4 to 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 these effects.

Impairment of liver and renal disease: See Section 4.2 **Dose and Method of Administration**.

Avoid contact with the skin and eyes.

Immunisation with live virus vaccines should only be undertaken with extreme caution (see Section 4.5 **Interactions with Other Medicines and Other Forms of Interactions**). Immunisation with oral poliovirus vaccines should be postponed in people in close contact with the patient, especially family members.

The bone marrow depressant effects of dacarbazine may result in an increased incidence of microbial infection, delayed healing and gingival bleeding. Dental work, whenever possible, should be completed prior to initiation of dacarbazine therapy, or deferred until blood counts have returned to normal. Patients should be instructed on proper oral hygiene during treatment, including caution in the use of toothbrushes, dental floss and toothpicks.

Use in the elderly
No data available.

Paediatric use
No data available.

Effects on laboratory tests
No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Microsomal liver enzyme inducers, e.g., barbiturates, rifampicin, phenytoin, may theoretically hasten the activation of dacarbazine to AIC.

Mercaptopurine, azathioprine, allopurinol: Dacarbazine inhibits xanthine oxidase and may theoretically potentiate the activity of these medicines.

The incidence or severity of side effects may be altered when dacarbazine is used in combination with other antineoplastic agents. The leucopenic and/or thrombocytopenic effects of dacarbazine may be increased with concurrent or recent therapy with other medications which cause these effects. Additive bone marrow depression may occur if dacarbazine is administered with other bone-marrow depressants or with radiation therapy. Dosage adjustment of dacarbazine may be necessary.

Sequential administration of dacarbazine (400 – 1000 milligrams/m^2) and fotemustine (100 milligrams/m^2) has been associated with acute lung toxicity, in the form of adult respiratory distress syndrome.

It has been reported that dacarbazine reduced the response to levodopa in a patient with Parkinson's disease. The mechanism of this interaction is unclear, but since the plasma levels of levodopa were unchanged, it is unlikely to be due to pharmacokinetic changes.

Administration of dacarbazine may potentiate the replication of live virus vaccines,

increase the adverse effects of the vaccine, or decrease the antibody response to the vaccine. Dacarbazine may also suppress the antibody response to killed virus vaccines. Viral vaccines should not be administered for 3 to 12 months after discontinuing immunosuppressive drug treatment.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility
No data available.

Use in pregnancy – Category D

Category D: This category specifies drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

The drug is teratogenic and carcinogenic when used in animals. When administered intraperitoneally to rats at doses of 50 or 70 milligrams/kg/day (approximately 11 times the human dose), teratogenic effects have been observed, including anomalies of the skeletal system, eyes, cardiovascular system and abdominal wall. Teratogenic effects have also been observed in rabbits administered 10 milligrams/kg intraperitoneally. No adequate and well controlled studies have been performed in pregnant women.

Dacarbazine for injection is therefore contraindicated in patients who are pregnant.

Use in lactation
It is not known whether dacarbazine is distributed into breast milk. Due to the potential risk to the infant, dacarbazine is contraindicated in breast-feeding mothers.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

More common reactions
Gastrointestinal: 90% of patients experience nausea and vomiting in the first two days of treatment. Diarrhoea may also occur. A degree of tolerance may develop to these effects after about 2 days of treatment. Vomiting lasts 1 to 12 hours. Prophylactic antiemetic therapy with a $5HT_3$ blocker or dexamethasone is usually required. Rarely, intractable nausea and vomiting have necessitated discontinuance of dacarbazine therapy.

Haematological: bone marrow depression (25%) (see Section 4.8 **Adverse Effects - Life threatening reactions**).

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 (i.e., 25 days after

completion of therapy). The average length of duration was 1 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.

Eosinophilia has been reported in one patient receiving dacarbazine.

Less common reactions
Cardiovascular: facial flushing, ECG abnormalities, orthostatic hypotension. Hypotension appears to be associated with high doses (>850 mg/m^2) of dacarbazine and may be dose-limiting.

Dermatological: (1%, usually transient) rash, alopecia. Photosensitivity reactions have occurred rarely.

General: (3%) flu-like syndrome 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 to 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 has been reported (see Section 4.4 **Special Warnings and Precautions for Use**) (0.01%). A case of acute hepatitis has been reported during the first course of dacarbazine. Granulomatous hepatitis has also occurred.

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

Local reactions: Injection of concentrated dacarbazine solutions may cause severe pain along the vein. Extravasation of the drug into surrounding tissue may cause severe pain, tissue damage and cellulitis.

Hypersensitivity: Anaphylaxis has occurred occasionally.

Dental effects: Dacarbazine may adversely affect dental procedures (see Section 4.4 **Special Warnings and Precautions for Use**).

Other: Dacarbazine may rarely cause stomatitis.

Life threatening reactions
Bone marrow depression: Death due to agranulocytosis or thrombocytopenia occurred in about 0.4% of patients in clinical trials.

Fatal hepatotoxicity: Budd-Chiari Syndrome (see Section 4.4 **Special Warnings and Precautions for Use**).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

Symptoms: Severe bone marrow depression and gastrointestinal effects such as nausea, vomiting and diarrhoea may be expected.

Treatment: There is no specific antidote to dacarbazine poisoning. Cease dacarbazine administration and institute supportive measures, e.g., appropriate transfusions, for bone marrow depression (see Section 4.8 **Adverse Effects - Haematological**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Relationship to other drugs: Dacarbazine is a structural analogue of 5-amino-imidazole-4-carboxamide which is an intermediate in purine biosynthesis.

Mechanism of action
This drug inhibits cell replication by an unknown mechanism. However, three possible mechanisms have been postulated:

1. 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.

2. One metabolite of dacarbazine, diazomethane, is an alkylating agent and may act in the same way as the nitrogen mustards.

3. The drug might act as a sulphydryl reagent since the inhibition of bacterial growth by dacarbazine can be prevented by glutathione.

Clinical trials
No data available.

5.2 Pharmacokinetic Properties

Absorption
Dacarbazine is poorly and erratically absorbed from the gastrointestinal tract, which could result in unpredictable tumour responses and possible increased toxicity. Therefore the drug is recommended for intravenous administration only. Peak plasma concentrations of about 8 micrograms per mL are reached immediately following administration of dacarbazine 4.5 milligrams/kg by intravenous push.

Distribution
The volume of distribution of dacarbazine exceeds total body water content, suggesting

localisation 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 human placenta or distributes into milk.

Metabolism
Dacarbazine is N-demethylated by liver microsomal enzymes to yield CO_2 which is excreted in expired air and aminoimidazole-carboxamide (AIC) which is excreted in the urine. About half the drug remains unchanged and is rapidly excreted by tubular secretion.

Excretion
As dacarbazine is approximately 50% metabolised by the liver and the remaining unchanged drug and metabolites are excreted in the urine, impairment of hepatic or renal function may require a reduction in dosage to avoid toxicity.

Plasma concentrations of dacarbazine appear to decline in a biphasic manner. The initial phase half-life ($t_{1/2\alpha}$) is very short, with one study reporting $t_{1/2\alpha}$ as 2.9 minutes. The terminal phase half-life ($t_{1/2\beta}$) is consistently longer 41.4 to 75 minutes. 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.

5.3 Preclinical Safety Data

Genotoxicity
No data available.

Carcinogenicity
The drug is teratogenic and carcinogenic when used in animals. When administered intraperitoneally to rats at doses of 50 or 70 milligrams/kg/day (approximately 11 times the human dose), teratogenic effects have been observed, including anomalies of the skeletal system, eyes, cardiovascular system and abdominal wall. Teratogenic effects have also been observed in rabbits administered 10 milligrams/kg intraperitoneally.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Citric acid monohydrate
Mannitol

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

Please refer to the outer carton for the expiry date.

Reconstituted vials are chemically stable for up to 8 hours if stored at 25°C and up to

24 hours if stored at 2°C to 8°C, protected from light. However, in order to reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C to 8°C for not more than 8 hours.

6.4 Special Precautions for Storage

Please refer to the outer carton for the recommended storage condition.
Refrigerate. Do not freeze. Protect from light.

6.5 Nature and Contents of Container

DBL™ Dacarbazine for Injection is a colourless or pale yellow crystalline powder, containing 200 mg dacarbazine filled in size 20 mL amber glass vial, single packs.

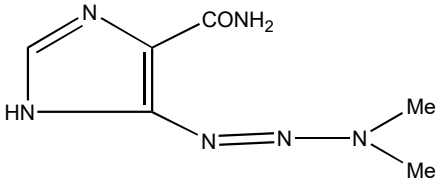
6.6 Special Precautions for Disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

If spill occurs, restrict access to the affected area. Wear two pairs of latex rubber gloves, a suitable mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towels or adsorbent granules. Spills may also be treated with 5% sodium hypochlorite. Collect the absorbent/adsorbent and other debris from the spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as toxic and hazardous and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second. Clean the remaining spill area with copious amounts of water.

6.7 Physicochemical Properties

Chemical structure
The molecular formula of dacarbazine is $C_6H_{10}N_6O$. Its molecular weight is 182.2. The structural formula of dacarbazine appears below:



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