# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

DACARBAZINE FOR INJECTION USP 200MG/VIAL

**ATC Code:** L01AX04
**Distribution Category:** POM

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each vial contains:
Dacarbazine USP 200mg
**Excipients: For a full list of excipients, see section 6.1**

## 3. PHARMACEUTICAL FORM:

Lyophilized powder for Injection
**Description:** A white to yellowish lyophilized mass.

## 4. CLINICAL PARTICULARS:

### 4.1 Therapeutic Indications

Dacarbazine is indicated for the treatment of patients with metastasized malignant melanoma.
Further indications for dacarbazine as part of a combination chemotherapy are:
- advanced Hodgkin's disease,
- advanced adult soft tissue sarcomas (except mesothelioma, Kaposi sarcoma).

### 4.2 Posology and method of administration

**Malignant Melanoma**
The recommended dosage is 2 to 4.5 mg/kg/day for 10 days. Treatment may be repeated at 4-week intervals.
An alternate recommended dosage is 250 mg/square meter body surface/day I.V injection for 5 days. Treatment may be repeated every 3 weeks.

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

### 4.3 Contraindications

Dacarbazine is contraindicated in patients: -

- who have a history of hypersensitivity reactions to dacarbazine or to any of the excipients.
- in pregnant or breastfeeding women
- in patients with leucopenia and/or thrombocytopenia

- in patients with severe liver or kidney diseases.

**4.4 Warning and Precautions**

It is recommended that dacarbazine should only be administered under the supervision of a physician specialized in oncology, having the facilities for regular monitoring of clinical, biochemical and hematological effects, during and after therapy.

If symptoms of a liver or kidney functional disorder or symptoms of a hypersensitivity reaction are observed immediate cessation of therapy is required. If veno-occlusive disease of the liver occurs, further therapy with dacarbazine is contra-indicated. Long-term therapy can cause cumulative bone marrow toxicity. The possible bone marrow depression requires careful monitoring of white blood cells, red blood cells and platelet levels. Hemopoetic toxicity may warrant temporary suspension or cessation of therapy. Extravasation of the drug during I.V. administration may result in tissue damage and severe pain. Furthermore, dacarbazine is a moderate immunosuppressive agent. Hepatotoxic drugs andalcohol should be avoided during chemotherapy

**4.5 Interactions with other medicinal products and other forms of interactions**

In case of previous or concomitant treatment having adverse effects on the bone marrow (particularly cytostatic agents, irradiation) myelotoxic interactions are possible. Studies to investigate the presence of phenotypic metabolism have not been undertaken but hydroxylation of the parent compound to metabolites with anti-tumor activity has been identified. Dacarbazine is metabolised by cytochrome P450 (CYP1A1, CYP1A2, and CYP2E1). This has to be taken into account if other drugs are co-administered which are metabolised by the same hepatic enzymes.

**4.6 Pregnancy and Lactation**

Dacarbazine has been shown to be mutagenic, teratogenic and carcinogenic in animals. It must be assumed that an increased risk for teratogenic effects exists in humans. Therefore, dacarbazine must not be used during pregnancy and during breastfeeding.

Women of child bearing potential:
Women of child bearing age must avoid pregnancy during dacarbazine treatment.

**4.7 Effect of ability to drive and use medicines**

Dacarbazine may influence the ability to drive or operate machines because of its central nervous side effects or because of nausea and vomiting.

**4.8 Undesirable effects**

Frequencies
Very common (> 1/10) Common (> 1/100, < 1/10) Uncommon (> 1/1,000, < 1/100)Rare (> 1/10,000, < 1/1,000)
Very rare (< 1/10,000), including isolated reports
The most commonly reported ADRs are gastrointestinal disorders (anorexia, nausea and vomiting) and blood and lymphatic system disorders as anemia, leukopenia and thrombocytopenia. The latter are dose-dependent and delayed, with the nadirs often only

occurring after 3 to 4 weeks.

| | |
|---|---|
| Infections and infestations | Uncommon (>1/1,000, <1/100) Infections |
| Blood and lymphatic systemdisorders | Common (> 1/100, < 1/10)<br>Anemia, leukopenia, thrombocytopeniaRare (> 1/10,000, < 1/1,000)<br>Pancytopenia, agranulocytosis |
| Immune system disorders | Rare (> 1/10,000, < 1/1,000) Anaphylactic reactions |
| Nervous system disorders | Rare (> 1/10,000, < 1/1,000)<br>Headaches, impaired vision, confusion, lethargy, convulsions, facial paranesthesia |
| Vascular disorders | Rare (> 1/10,000, < 1/1,000) Facial flushing |
| Gastrointestinal disorders | Common (> 1/100, < 1/10)<br>Anorexia, nausea, vomiting<br>Rare (> 1/10,000, < 1/1,000)<br>Diarrhoea |
| Hepatobiliary disorders | Rare (> 1/10,000, < 1/1,000)<br>Hepatic necrosis due to veno-occlusive disease(VOD) of the liver |
| Renal and urinary disorders | Rare (> 1/10,000, < 1/1,000)<br>Impaired renal function |
| Skin and subcutaneous tissuedisorders | Uncommon (> 1/1,000, < 1/100)<br>Alopecia, hyperpigmentation, photosensitivityRare (> 1/10,000, < 1/1,000)<br>Erythema, maculopapular exanthema, urticaria |
| General disorders andadministration site conditions | Uncommon (> 1/1,000, < 1/100)Flu-like symptoms<br>Rare (> 1/10,000, < 1/1,000)<br>Application site irritation |
| Investigations | Rare (> 1/10,000, < 1/1,000)<br>Elevation of liver enzymes |

Disturbances of the digestive tract such as anorexia, nausea and vomiting are common and severe. In rare cases diarrhoea has been observed.

Changes in blood counts often observed (anemia, leukopenia, thrombocytopenia) are dose-dependent and delayed, with the nadirs often only occurring after 3 to 4 weeks. In rare cases pancytopenia and agranulocytosis have been described.
Flu-like symptoms with exhaustion, chills, fever and muscular pain are occasionally observed during or often only days after dacarbazine administration. These disturbances may recur with the next infusion.
Elevation of liver enzymes (e.g., alkaline phosphatase) is observed in rare cases.

Rarely liver necrosis due to occlusion of intrahepatic veins (veno-occlusive disease of the liver) has been observed after administration of dacarbazine in monotherapy or in combined treatment modalities. In general, the syndrome occurred during the second cycle of therapy. Symptoms included fever, eosinophilia, abdominal pain, enlarged liver, jaundice and shock which worsened rapidly over a few hours or days. As fatal outcome has been described special care has to be taken of frequently monitoring of liver size, function and blood counts (especially eosinophils). In single cases of suspected veno-occlusive disease early therapy with high-dose corticosteroids (for example hydrocortisone 300 mg/day) with or without fibrinolytic agents like heparin or tissue plasminogen activator was successful.

Application site irritations and some of the systemic adverse reactions are thought to result from formation of photodegradation products.

Impaired renal function with increased blood levels of substances obligatory excreted by urine is rare.

Central nervous side effects such as headaches, impaired vision, confusion, lethargy and convulsions rarely may occur. Facial paranesthesia and flushing may occur shortly after injection.

Allergic reactions of the skin in the form of erythema, maculopapular exanthema or urticaria are observed rarely. Infrequently alopecia, hyperpigmentation and photosensitivity of the skin may occur. In rare cases anaphylactic reactions have been described.

Inadvertent paravenous injection is expected to cause local pain and necrosis.

### 4.9 Overdose

Severe bone marrow suppression, bone marrow aplasia occurs due to overdose.Give supportive treatment and monitor blood cell counts.

## 5. PHARMACOLOGICAL PROPERTIES:

### 5.1 Pharmacodynamic properties

Dacarbazine is a cytostatic agent: The antineoplastic effect is due to an inhibition of cell growth which is independent of the cell cycle and due to an inhibition of DNA synthesis. An alkylating effect has also been shown and other cytostatic mechanisms may also be

influenced by dacarbazine.

Dacarbazine is considered not to show an antineoplastic effect by itself. However, by microsomal N-demethylation it is quickly converted to 5-aminoimidazole- 4- carboxamide and a methyl cation, which is responsible for the alkylating effect of the drug.

**5.2 Pharmacokinetic properties**

After intravenous application dacarbazine is quickly distributed into tissue. Plasma protein binding is 5%. Kinetics in plasma is biphasic; the initial (distribution) half-life is only 20 minutes; terminal half-life is 0.5 - 3.5 hours. Dacarbazine is inactive until metabolised in the liver by cytochromes P450 to form the reactive N- demethylated species HMMTIC and MTIC. This is catalyzed by CYP1A1, CYP1A2,and CYP2E1. MTIC is further metabolised to 5-aminoimidazole-4-carboxamide (AIC). Dacarbazine is metabolized mainly in the liver by both hydroxylation and demethylation, approx. 20-50% of the drug are excreted unmodified by the kidney via renal tubular secretion.

**5.3 Pre-clinical safety data**

Because of its pharmacodynamic properties dacarbazine shows mutagenic, carcinogenic and teratogenic effects which are detectable in experimental test systems.

## 6. PHARMACEUTICAL PARTICULARS:

**6.1 List of excipients**

Citric acid Anhydrous, Mannitol, Sodium Hydroxide and Water for Injections.

**6.2 Incompatibilities**

None

**6.3 Shelf life**

24 Months

**6.4 Special precautions for storage**

Store below $2^0$C-$8^0$C. Protect from light.

**6.5 Nature and contents of container**

20ml 20mm amber Type I vial.

**6.6 Instructions for use**

Any unused product or waste material should be disposed of in accordance withlocal requirements.'

**Reconstitution**

| Dacarbazine for injection | Desired concentration | Sterile Water for Injection volume to be added |
|---|---|---|
| 100mg | 10mg/ml | 10ml |
| 200mg | 10mg/ml | 20ml |
| 500mg | 10mg/ml | 50ml |
| 1gm | 10mg/ml | 50ml |

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, or sodium chloride injection, 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 8hours. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection, 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. Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration whenever solution and container permit.

**7. MAKETING AUTHORIZATION HOLDER:**

**8.** Miracalus Pharma Pvt.Ltd
213, Shivai Dongre Industrial Premises,
Andheri Kurla Rd, Andheri (E), Mumbai 400 072

**Manufactured in India by:**
G-17/1, M.I.D.C., Boisar, Dist - Thane (INDIA)

**9. MARKETING AUTHORIZATION NUMBER**
TAN 21 HM 0055

**10. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

24/12/2020

**11. DATE OF REVISION OF THE TEXT:**

March 2021