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Prescribing Information

DACARBAZINE MEDAC 200 mg / 500 mg / 1000 mg

1. Name of the Medicinal Product

Dacarbazine medac 200 mg, Powder for solution for injection or infusion
Dacarbazine medac 500 mg, Powder for solution for infusion
Dacarbazine medac 1000 mg, Powder for solution for infusion

2. Qualitative and Quantitative Composition

Each single-dose vial of Dacarbazine medac 200 mg / 500 mg / 1000 mg contains 200 mg / 500 mg / 1000 mg dacarbazine (as dacarbazine citrate, formed in situ).

After reconstitution Dacarbazine medac 200 mg contains 10 mg/ml dacarbazine (see 6.6. a).

After reconstitution and final dilution Dacarbazine medac 500 mg / 1000 mg contains 1.4 – 2.0 mg/ml (2.8 – 4.0 mg/ml) dacarbazine (see 6.6. b).

For excipients, see section 6.1.

3. Pharmaceutical Form

Dacarbazine medac 200 mg: Powder for solution for injection or infusion.
Dacarbazine medac 500 mg / 1000 mg: Powder for solution for infusion.
Dacarbazine medac is a white or pale yellow powder.

CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dacarbazine is indicated for the treatment of patients with metastatic malignant melanoma. Further indication for dacarbazine as part of a combination chemotherapy in advanced Hodgkin's disease, as a second line.

4.2 Posology and Method of Administration

The use of dacarbazine should be confined to physicians experienced in oncology or hematology respectively.

Dacarbazine is sensitive to light exposure. All reconstituted solutions should be suitably protected from light also during administration (light-resistant infusion set).

Care should be taken of administration of the injection to avoid extravasation into tissues since this will cause local pain and tissue damage. If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should be introduced into another vein.

The following regimes can be used. For further details cf. current scientific literature.

Malignant Melanoma

Dacarbazine can be administered as single agent in doses of 200 to 250 mg/m² body surface area/day as an i.v. injection for 5 days every 3 weeks.

As an alternative to an intravenous bolus injection dacarbazine can be administered as a short-term infusion (over 15 - 30 minutes).

It is also possible to give 850 mg/m² body surface area on day 1 and then once every 3 weeks as intravenous infusion.

Hodgkin's Disease

Dacarbazine is administered in a daily dose of 375 mg/m² body surface area i.v. every 15 days in combination with doxorubicin, bleomycin and vinblastine (ABVD regimen).

During dacarbazine treatment frequent monitoring of blood counts should be conducted as well as monitoring of hepatic and renal function. Since severe gastrointestinal reactions frequently occur, antiemetic and supportive measures are advisable.

Because severe gastrointestinal and hematological disturbances can occur an extremely careful benefit-risk analysis has to be made before every course of therapy with dacarbazine.

Duration of therapy

The treating physician should individually decide about the duration of therapy taking into account the type and stage of the underlying disease, the combination therapy administered and the response to and adverse effects of dacarbazine. In advanced Hodgkin's disease, a usual recommendation is to administer 6 cycles of ABVD combination therapy. In metastasized malignant melanoma and in advanced tissue sarcoma, the duration of treatment depends on the efficacy and tolerability in the individual patient.

Rate of administration

Doses up to 200 mg/m² may be given as a slow intravenous injection. Larger doses (ranging from 200 to 850 mg/m²) should be administered as an i.v. infusion over 15-30 minutes.

It is recommended to test the patency of the vein first with a 5- to 10-ml flush of sodium chloride infusion solution or glucose 5%. The same solutions should be used after infusion to flush any remaining drug from the tubing.

After reconstitution with water for injection without further dilution with sodium chloride infusion solution or glucose 5 %, dacarbazine 200 mg preparation is hypo-osmolar (ca. 100mOsmol/kg) and should therefore be given by slow intravenous injection e.g. over 1 minute rather than rapid intravenous bolus over a few seconds.

Special populations

Patients with kidney/liver insufficiency:

If there is mild to moderate renal or hepatic insufficiency alone, a dose reduction is not usually required. In patients with combined renal and hepatic impairment elimination of dacarbazine is prolonged. However, no validated recommendations on dose reductions can be given currently.

Elderly patients:

As limited experience in elderly patients is available no special instructions for the use in elderly patients can be given.

Children:

No special recommendations for the use of dacarbazine in the paediatric age group can be given until further data become available.

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 Special Warnings and Special Precautions for Use

It is recommended that dacarbazine should only be administered under the supervision of a physician specialised in oncology, having the facilities for regular monitoring of clinical, biochemical and haematological 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.

Note: The responsible physician should be aware of a rarely observed severe complication during therapy resulting from liver necrosis due to occlusion of intrahepatic veins. Therefore frequent monitoring of liver size, function and blood counts (especially eosinophils) is required. 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 (see 4.8).

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 and alcohol should be avoided during chemotherapy.

Contraceptive measures:

Men are advised to take contraceptive measures during and for 6 months after cessation of therapy.

Administration of dacarbazine in the paediatric age group: Dacarbazine is not recommended for use in the paediatric age group until further data become available.

Handling of dacarbazine:

Dacarbazine should be handled according to standard procedures for cytostatics that have mutagenic, carcinogenic and teratogenic effects.

4.5 Interaction with other medicinal products and other forms of interaction

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-tumour 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.

Dacarbazine can enhance the effects of methoxypsoralen because of photosensitization.

4.6 Use during Pregnancy and Lactation

Pregnancy/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 (see: 4.3 and 4.4.).

Women of child bearing potential:

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

4.7 Effects on Ability to Drive and Use Machines

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	<u>Uncommon (>1/1,000, <1/100)</u> Infections
Blood and lymphatic system disorders	<u>Common (>1/100, <1/10)</u> Anemia, leukopenia, thrombocytopenia <u>Rare (>1/10,000, <1/1,000)</u> <u>Pancytopenia, agranulocytosis</u>
Immune system disorders	<u>Rare (>1/10,000, <1/1,000)</u> Anaphylactic reactions
Nervous system disorders	<u>Rare (>1/10,000, <1/1,000)</u> Headaches, impaired vision, confusion, lethargy, convulsions, facial paraesthesia
Vascular disorders	<u>Rare (>1/10,000, <1/1,000)</u> <u>Facial flushing</u>
Gastrointestinal disorders	<u>Common (>1/100, <1/10)</u> Anorexia, nausea, vomiting <u>Rare (>1/10,000, <1/1,000)</u> Diarrhoea
Hepatobiliary disorders	<u>Rare (>1/10,000, <1/1,000)</u> Hepatic necrosis due to veno-occlusive disease (VOD) of the liver
Renal and urinary disorders	<u>Rare (>1/10,000, <1/1,000)</u> Impaired renal function
Skin and subcutaneous tissue disorders	<u>Uncommon (>1/1,000, <1/100)</u> Alopecia, hyperpigmentation, photosensitivity <u>Rare (>1/10,000, <1/1,000)</u>

	Erythema, maculopapular exanthema, urticaria
General disorders and administration site conditions	<u>Uncommon (>1/1,000, <1/100)</u> Flu-like symptoms <u>Rare (>1/10,000, <1/1,000)</u> Application site irritation
Investigations	<u>Rare (>1/10,000, <1/1,000)</u> 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 (see 4.2 and 4.4).

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 paraesthesia 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.

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

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at the following link:

<https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

In addition, you may report by sending an e-mail message to safety@tzamal-medical.co.il or by visiting the "Contact Us" webpage at: <http://www.tzamal-medical.co.il/69601.html> or by phone: +972-73-7151107

4.9 Overdose

The primary anticipated complications of overdose are severe bone marrow suppression, eventually bone marrow aplasia which may be delayed by up to two weeks.

Time to occurrence of nadirs of leucocytes and thrombocytes can be 4 weeks. Even if overdosage is only suspected, long-term careful hematologic monitoring is essential. There is no known

antidote for dacarbazine overdose. Therefore, special care has to be taken to avoid overdose of this drug.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Alkylating agents, ATC code: L01AX04.

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-amino-imidazole-4-carboxamide and a methyl cation, which is responsible for the alkylating effect of the drug.

5.2 Pharmacokinetic Properties

After intravenous administration dacarbazine is quickly distributed into tissue. Plasma protein binding is 5%. Kinetics in plasma are 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 catalysed 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 is excreted unmodified by the kidney via renal tubular secretion.

5.3 Preclinical Safety Data

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

PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Citric acid, anhydrous and mannitol.

6.2 Incompatibilities

Dacarbazine-solution is chemically incompatible with heparin, hydrocortisone, L-cysteine and sodium hydrogen carbonate.

6.3 Shelf Life

The shelf-life is 3 years.

Shelf life of the reconstituted solution of Dacarbazine medac 200 mg:

A chemical and physical in-use stability has been demonstrated for 24 hours at 20°C protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would normally be no longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Shelf life of the reconstituted and further diluted solution of Dacarbazine medac 200 mg:
The reconstituted and further diluted solution must be used immediately.

Shelf life of the reconstituted and further diluted solution of Dacarbazine medac 500 mg / 1000 mg:
The reconstituted and further diluted solution must be used immediately.

6.4 Special Precautions for Storage

Do not store above 25 °C, keep the vial in outer carton in order to protect from light. Reconstituted solutions should also be protected from light.
For storage of the reconstituted product, see 6.3.

6.5 Nature and Contents of Container

Dacarbazine medac 200 mg is supplied as a sterile powder for solution for injection or infusion in single-dose vials made of amber glass (Type I, Ph.Eur.) and closed with butyl rubber stoppers. Each carton of Dacarbazine medac 200 mg contains 1 vial or 10 vials.

Dacarbazine medac 500 mg (-1000 mg) is supplied as a sterile powder for solution for infusion in single-dose vials made of amber glass (Type I, Ph.Eur.) and closed with butyl rubber stoppers. Each carton of Dacarbazine medac 500 mg (-1000mg) contains 1 vial or 10 vials.

Not all pack sizes may be marketed.

6.6 Instructions for Use, Handling and Disposal

Recommendations for the safe handling:

Dacarbazine is an antineoplastic agent. Before commencing, local cytotoxic guidelines should be referred to.

Dacarbazine should only be opened by trained staff and as with all cytotoxic agents, precautions should be taken to avoid exposing staff. Handling of cytotoxic drugs should be generally avoided during pregnancy. Preparation of solution for administration should be carried out in a designated handling area and working over a washable tray or disposable plastic-backed absorbent paper.

Suitable eye protection, disposable gloves, face mask and disposable apron should be worn. Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).

On completion, any exposed surface should be thoroughly cleaned and hands and face washed.

In the event of spillage, operators should put on gloves, face masks, eye-protection and disposable apron and mop up the spilled material with an absorbent material tapped in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin or sealed for incineration.”

Preparation for the intravenous administration:

Dacarbazine-solutions are prepared immediately before use.

Dacarbazine is sensitive to light exposure. During administration, the infusion container and administration set should be protected from exposure to daylight, e.g. by using light-resistant PVC-infusion sets. Normal infusion sets should be wrapped up in e.g. UV-resistant foils.

a) Preparation of Dacarbazine medac 200 mg:

Aseptically transfer the required amount of water for injections (Dacarbazine medac 200 mg: 20 ml) into the vial and shake until a solution is obtained. This freshly prepared solution (Dacarbazine: 10 mg/ml*) is administered as a slow injection.

For preparation of Dacarbazine medac 200 mg for i.v. infusion the freshly prepared solution is further diluted with 200-300 ml sodium chloride infusion solution or glucose 5%. This solution is given as a short term infusion over a period between 15 - 30 minutes.

b) Preparation of Dacarbazine medac 500 mg / 1000 mg:

Aseptically transfer the required amount of 50 ml water for injection into the Dacarbazine medac 500 mg / 1000 mg vial and shake until a solution is obtained*. The resulting solution has to be further diluted with 200 - 300 ml sodium chloride infusion solution or glucose 5%. The obtained infusion solution is ready for i. v. administration (Dacarbazine medac 500 mg: 1.4 - 2.0 mg/ml; Dacarbazine medac 1000 mg: 2.8 - 4.0 mg/ml) and should be given within 20 - 30 minutes.

Dacarbazine medac 200 mg / 500 mg / 1000 mg is for single use only.

The diluted solution for infusion should be visually inspected and only clear solutions practically free from particles should be used. Do not use the solution if particles are present.

Any portion of the contents remaining after use should be discarded, as well as solutions where the visual appearance of the product has changed.

Disposal: All materials that have been utilized for dilution and administration should be disposed of according to standard procedures (incineration).

* Density of the solution:

$$\rho = 1.007 \text{ mg/ml}$$

+ Density of the solution:

$$\rho = 1.007 \text{ mg/ml (Dacarbazine medac 500 mg)}$$

$$\rho = 1.015 \text{ mg/ml (Dacarbazine medac 1000 mg)}$$

Registration Number: Dacarbazine medac 200 mg: 134.88.31170.00/01
Dacarbazine medac 500 mg: 134.89.31171.00
Dacarbazine medac 1000 mg: 134.90.31172.00/01

Manufacturer: medac (medac Gesellschaft fuer klinische Spezialpraeparate mbH), Germany.

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