1. NAME OF THE MEDICINAL PRODUCT

DACARBAZINE-DACIN 200 mg

2. COMPOSITION

Active substance: dacarbazine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vial containing 200 mg dacarbazine powder for solution for injection/infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Metastatic, malignant melanoma.

Hodgkin's disease as a second line therapy when used in combination with other agents.

4.2. Posology and method of administration

Unless specific dosage guidelines for combination therapy have been specified, the following dosage regimens are to be followed, particularly for monotherapy: 4-5 day cycles of 150 to 250 mg/m2 body surface area/day I.V.
This treatment can be repeated every 21 days. Alternatively, 2.0-4.5 mg/kg/day I.V may be given for 1-10 days. This regimen can be repeated every 28 days.
DACARBAZINE-DACIN 200 mg is administered either as an intravenous injection over approximately one minute or as an intravenous infusion over 15-30 minutes. If necessary, DACARBAZINE-DACIN 200 mg can be given intra-arterially.

Combination chemotherapy: generally 4 to 5 day cycles of 100 mg/m^2/day, with a 21 day interval between subsequent cycles starting from the last day of treatment.

For the preparation of the solution for injection/infusion, please refer to section 6.4.
Extravasation of DACARBAZINE-DACIN 200 mg during intravenous administration can induce tissue damage and severe pain.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe renal or hepatic impairment.
- Leukopenia, thrombocytopenia.
- Pregnancy, breast-feeding.

4.4. Special warnings and precautions for use

DACARBAZINE-DACIN 200 mg is haematotoxic and haematotoxicity may be cumulative during prolonged therapy. Impairment of haematopoiesis mainly affects leukocytes and platelets. The nadir is reached after approximately 21–25 days. Leukopenia and thrombocytopenia can be serious and may have a fatal outcome. The blood count must be closely monitored during therapy with DACARBAZINE-DACIN 200 mg. Temporary

suspension or discontinuation of DACARBAZINE-DACIN 200 mg therapy may be required. During therapy with DACARBAZINE-DACIN 200 mg, hepatic enzymes, liver size and creatinine must be regularly monitored. Serious complications, such as liver necrosis and veno-occlusive disease (VOD), have been observed. Treatment must be discontinued immediately if signs of hepatic or renal dysfunction occur. If VOD occurs, further therapy with DACARBAZINE-DACIN 200 mg is contraindicated.
Vaccinations given during DACARBAZINE-DACIN 200 mg therapy may be ineffective due to immunosuppression. Vaccinations with live vaccines are not recommended due to the risk of infection.
Extravasation may result in tissue damage and severe pain.

Contraceptive measures:
Due to the genotoxic potential of dacarbazine (see 5.3 “Preclinical data”), women of childbearing potential must use effective contraceptive measures while being treated with DACARBAZINE-DACIN 200 mg and for 6 months following completion of treatment.
Men are recommended to use effective contraceptive measures and to not father a child while receiving DACARBAZINE-DACIN 200 mg and for 3 months following completion of therapy.
Patients considering pregnancy should seek genetic counselling after the period of contraceptive use (see 4.6 Fertility, pregnancy and breast-feeding).

4.5. Interaction with other medicinal products and other forms of interaction

No studies have been performed to investigate interactions with other medicinal products. If DACARBAZINE-DACIN 200 mg is used concomitantly with other antineoplastic agents, toxicity, in particular haematotoxicity, may be potentiated. Medicinal products with hepatotoxic potential and alcohol are contraindicated during treatment with DACARBAZINE-DACIN 200 mg.

4.6. Fertility, pregnancy and breast-feeding

Pregnancy
Dacarbazine has been demonstrated to have a mutagenic, teratogenic and carcinogenic effects in animals. An increased teratogenic risk in humans must therefore also be assumed. No controlled human studies have been performed. DACARBAZINE-DACIN 200 mg may not be administered during pregnancy.

Contraception in men and women
Due to the genotoxic potential of dacarbazine (see 5.3 “Preclinical safety data”), women of childbearing potential must use effective contraceptive measures while being treated with DACARBAZINE-DACIN 200 mg and for 6 months following completion of treatment.
Men are recommended to use effective contraceptive measures and to not father a child while receiving DACARBAZINE-DACIN 200 mg and for 3 months following completion of treatment.

Breast-feeding
It is not known whether dacarbazine passes into breast milk. Women may not breastfeed during treatment with DACARBAZINE-DACIN 200 mg.

Fertility
Due to the genotoxic potential of dacarbazine, patients are advised to seek advice on fertility preservation options before starting treatment with dacarbazine. After treatment with dacarbazine, patients planning pregnancy are advised to seek genetic counselling.

4.7. Effects on ability to drive and use machines

No studies on the effect of dacarbazine on the ability to drive and use machines have been performed. Due to the undesirable effects of DACARBAZINE-DACIN 200 mg, such as nausea and vomiting, caution is advised when driving and using machines.

4.8. Undesirable effects

The most serious adverse effect of DACARBAZINE-DACIN 200 mg is bone marrow suppression with leukopenia, thrombocytopenia and, to a lesser degree, anaemia. The most common undesirable effects are anorexia, nausea and vomiting (>90%) and occur particularly at the start of treatment. Vomiting can persist for 1–12 hours.
The adverse effects are classified by MedDRA system organ classes and frequency according to the following convention: “very common” (≥1/10), “common” (≥1/100, <1/10), “uncommon” (≥1/1000, <1/100), “rare” (≥1/10'000, <1/1000), “very rare” (<1/10'000) and “not known” (cannot be estimated from the available data).

Blood and lymphatic system disorders
Common: leukopenia, thrombocytopenia, anaemia.

Immune system disorders
Very rare: anaphylaxis.

Metabolism and nutrition disorders
Very common: anorexia (>90%).

Nervous system disorders
Rare: facial paraesthesia, headache, seizures.

Eye disorders
Uncommon: blurred vision.
Vascular disorders
Uncommon: flush.
Not known: hypotension (at doses >850 mg/m^2).

Gastrointestinal disorders
Very common: nausea (>90%), vomiting (>90%).
Rare: diarrhoea.

Hepatobiliary disorders
Rare: liver dysfunction.
Very rare: liver necrosis, veno-occlusive disease.

Skin and subcutaneous tissue disorders
Rare: alopecia, maculopapular exanthema, urticaria, hyperpigmentation.

Musculoskeletal and connective tissue disorders
Uncommon: muscular pain.

Renal and urinary disorders
Rare: renal failure, increased creatinine.

General disorders and administration site conditions
Fever (up to 39°C), malaise, flu-like syndrome, administration site pain, tissue damage and severe pain in the event of extravasation.

Reporting suspected adverse reactions
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:
https://sideeffects.health.gov.il

4.9. Overdose

Severe bone marrow suppression is likely in the event of overdosage. Leukocyte and platelet nadir values may occur after 4 weeks. Hypotensive episodes have been observed following use of high dacarbazine doses (>850 mg/m2) (see “Undesirable effects”). If hypotension occurs, supportive therapy is recommended, e.g. hydration with 500 mL normal saline solution. There is no specific antidote for dacarbazine. Utmost caution must therefore be exercised each time it is administered, in order to avoid overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Alkylating agents, ATC code: L01AX04.

Mechanism of action
Dacarbazine is an antineoplastic imidazole carboxamide derivative (dimethyl triazeno imidazole carboxamide, DTIC). It represents a prodrug, and the effect is mediated via its active metabolite monomethyl triazeno imidazole carboxamide (MTIC).

Pharmacodynamics
MTIC inhibits DNA synthesis independently of the cell cycle. Alkylation and interaction with SH groups contribute to the cytostatic effect.

5.2. Pharmacokinetic properties

Distribution
Dacarbazine is only minimally bound to plasma proteins (5%). Its volume of distribution is 1.49 L/kg. Dacarbazine passes the blood-brain barrier, and its concentration in cerebrospinal fluid is 14% of plasma concentrations. After IV administration, the distribution half-life is approximately 19-38 minutes.

Metabolism

Dacarbazine is metabolised in the liver by CYP isoenzymes to the active monomethyl triazeno imidazole carboxamide (MTIC). This is spontaneously degraded (with the formation of a methyl cation) to aminoimidazole carboxamide (AIC), its inactive main metabolite, which also occurs as an intermediate product of purine biosynthesis. Other metabolites are adenine, hypoxanthine, xanthine and uric acid.

Elimination

18–63% of a single dose is excreted via the kidneys by glomerular filtration and

tubular secretion, approximately half of which as unchanged dacarbazine. The elimination half-life is 5 hours.

Kinetics in specific patient groups

Hepatic impairment

In patients with hepatic impairment, the elimination half-life is prolonged.

Renal impairment

In patients with renal impairment, the elimination half-life is prolonged.

Elderly patients

Pharmacokinetic data are limited for elderly patients.

Paediatric population

Pharmacokinetic data are limited for children and adolescents.

5.3. Preclinical safety data

Mutagenicity
In animal experimental studies, dacarbazine had mutagenic effects.

Carcinogenicity
In animal experimental studies, dacarbazine had carcinogenic effects.

Reproductive toxicity
In animal experimental studies, dacarbazine had teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid monohydrate, mannitol.

6.2. Incompatibilities

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

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Reconstitution & dilution of the product

Shelf life and storage conditions after reconstitution:

The reconstituted solution for injection does not contain any preservative. Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature and under light protection and for 5 days at 2 to 8°C and under light protection. From a microbiological point of view, the reconstituted solution should be used immediately. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to

use are the responsibility of the user and would normally not be longer than 24 hours in a refrigerator (2 to 8°C) and protected from light, unless the reconstitution has taken place under controlled and validated aseptic conditions.

Shelf life and storage conditions after dilution:

The diluted solution for infusion does not contain any preservatives.
Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature and under light protection and for 5 days at 2 to 8°C and under light protection. From a microbiological point of view, the diluted solution for infusion should be used immediately. If the diluted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours in a refrigerator (2 to 8°C) and protected from light, unless the reconstitution and dilution have taken place under controlled and validated aseptic conditions.

Once prepared, solutions must be stored in light proof containers and administered using a light proof delivery system (such as a non-transparent, light proof delivery tube (use of aluminium foil).

6.5. Special precautions for storage

DACARBAZINE-DACIN 200 mg must be stored in its original packaging, protected from light and below 25°C.
It should be kept out of the reach of children.

6.6. Handling of cytostatic agents

When handling DACARBAZINE-DACIN 200 mg, preparing the solution for injection/infusion or when disposing of any remaining solution, the standard procedures for handling cytostatic agents are to be followed.

6.7. Package

Presentations: 10 and 12 brown glass vials (Type I).

Not all the package sizes may be marketed.

7. MANUFACTURER

Lipomed AG Fabrikmattenweg 4 CH-4144 Arlesheim Switzerland

8. LICENSE HOLDER AND IMPORTER

Propharm Ltd, POB. 4046, Ben Gurion 23, Zichron Ya'akov 30900

Reg. No.: 137-62-31369-00

Revised in August 2025.