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 is administered either as an intravenous injection over approximately one minute or as an intravenous infusion over 15-30 minutes. If necessary, DACARBAZINE-DACIN can be given intra-arterially.

Combination Chemotherapy: generally 4 to 5 day cycles of 100 mg/m2/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 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,
- pregnancy or breastfeeding (see Section 4.6),
- leukopenia and/or thrombocytopenia,
- severe liver or kidney diseases.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

It is recommended that dacarbazine should only be administered under the supervision of a physician specialised in oncology who has 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 contraindicated.

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 Section 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. Haemopoietic toxicity may warrant temporary suspension or cessation of therapy.

Extravasation of the medicinal product during I.V. administration may result in tissue damage and severe pain.
Concomitant use with phenytoin should be avoided because reduced absorption of phenytoin from the gastrointestinal tract may predispose the patient to convulsions (see Section 4.5).

Dacarbazine is a moderate immunosuppressive agent. Administration of live vaccines to patients who are immunocompromised as a result of treatment with chemotherapeutics such as dacarbazine can cause serious and potentially fatal infections. Immunisation with live vaccines should therefore be avoided during dacarbazine therapy. It is generally advised to use live virus vaccines with caution after stopping chemotherapy and to take the patient's immune status into account, depending also on the disease and other therapies. Vaccination with live vaccines should be administrated no sooner than 3 months after the completion of chemotherapy. Inactivated vaccines can be used if available.

Concomitant use of fotemustine can cause acute pulmonary toxicity (adult respiratory distress syndrome), which may lead to a fatal outcome. Fotemustine and dacarbazine should not be used concomitantly.

Hepatotoxic medicinal products 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.

Paediatric population:
Dacarbazine is not recommended for use in the paediatric age group until further data become available. For precaution on handling, please see Section 6.5 and 6.6.

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 medicinal products are co-administered which are metabolised by the same hepatic enzymes.

Dacarbazine can enhance the effects of methoxypsoralen because of photosensitization.

Immunisation with live vaccines should be avoided during therapy with dacarbazine due to the risk of serious and potentially fatal infections. It is advised to use live virus vaccines with caution after stopping chemotherapy and vaccinate not sooner than 3 months after the last dose of chemotherapy. It is recommended to use an inactivated vaccine if available (see also Section 4.4).

Risk of thrombosis is increased in malignant diseases; therefore, use of concomitant anticoagulation is common. If the patient is to receive oral anticoagulants, the frequency of INR monitoring must be increased due to large inter-individual variability in coagulation and due to possible interaction between anticoagulants and cytostatics.

Concomitant use with phenytoin may cause reduced absorption of phenytoin from the gastrointestinal tract and may predispose the patient to convulsions (see Section 4.4).

Concomitant use of cyclosporine (and in some cases tacrolimus) must be considered carefully because these agents may cause excessive immunosuppression and lympho-proliferation.

Concomitant use of fotemustine can cause acute pulmonary toxicity (adult respiratory distress syndrome). Fotemustine and dacarbazine should not be used concomitantly.

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy
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- DACI is contraindicated during pregnancy (see Section 4.3).

Women of childbearing potential have to use effective contraception during treatment.

Breast-feeding
DACARBAZINE- DACIN is contraindicated during breast-feeding (see Section 4.3).

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 to< 1/10)
Uncommon (> 1/1,000 to< 1/100)
Rare (> 1/10,000 to< 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

The most commonly reported ADRs are gastrointestinal disorders (anorexia, nausea and vomiting) and blood and lymphatic system disorders such as anaemia, 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 Infections
Blood and lymphatic system disorders	Common Anaemia, leukopenia, thrombocytopenia Rare Pancytopenia, agranulocytosis
Immune system disorders	Rare Anaphylactic reactions
Nervous system disorders	Rare Headaches, impaired vision, confusion, lethargy, convulsions, facial paraesthesia
Vascular disorders	Rare Facial flushing Not known: hypotension (at doses >850 mg/m^2).
Gastrointestinal disorders	Common Anorexia, nausea, vomiting Rare Diarrhoea
Hepatobiliary disorders	Rare Hepatic necrosis due to veno-occlusive disease (VOD) of the liver, Budd-Chiari syndrome (with potentially fatal outcome)
Renal and urinary disorders	Rare Impaired renal function
Skin and subcutaneous tissue disorders	Uncommon Alopecia, hyperpigmentation, photosensitivity Rare Erythema, maculopapular exanthema, urticaria

General disorders and administration site conditions	Uncommon Flu-like symptoms Rare Application site irritation
Investigations	Rare Hepatic enzymes increased (e.g. alkaline phosphatase, ASAT, ALAT), blood lactate dehydrogenase (LOH) increased, blood creatinine increased, blood urea increased

Description of selected adverse reactions

Changes in blood counts often observed (anaemia, leukopenia, thrombocytopenia) are dose-dependent and delayed, with the nadirs often only occurring after 3 to 4 weeks.
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.

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 (see Section 4.4).

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

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.

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

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

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 medicinal product.

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.

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 medicinal product.

5.2. PHARMACOKINETIC PROPERTIES

Distribution

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.

Biotransformation

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).

Elimination

Dacarbazine is metabolised mainly in the liver by both hydroxylation and demethylation, approx. 20 - 50 % of the medicinal product 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.

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 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, 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 presentations are marketed in the country.

7. MANUFACTURER

LIPOMED AG
FABRIKMATTENWEG 4
CH-4144 ARLESHEIM
SWITZERLAND

8. LICENSE HOLDER AND IMPORTER

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

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