# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Dacarbazine Lipomed 500 mg powder for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial of Dacarbazine Lipomed 500 mg contains 500 mg dacarbazine (as dacarbazine citrate, formed *in situ*).

After reconstitution of Dacarbazine Lipomed 500 mg with 50 ml of water for injections, 1 ml of solution contains 10 mg dacarbazine (see section 6.6).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for solution for infusion.
White lyophilized powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Dacarbazine Lipomed 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

Treatment with Dacarbazine Lipomed should only be carried out by physicians experienced in oncology or haematology respectively.

During treatment with Dacarbazine Lipomed, frequent monitoring of blood counts as well as monitoring of hepatic and renal function are required. Since severe gastrointestinal reactions frequently occur, anti-emetic and supportive measures are advisable.

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

Food intake prior to administration of Dacarbazine Lipomed should be avoided to reduce the severity of nausea and vomiting. Excreta and vomit should be handled with care.

Posology
The following regimes can be used. For further details, see current scientific literature.

*Malignant melanoma*
Dacarbazine can be administered as single agent in doses of 200 to 250 mg/m$^2$ body surface area/day intravenously for 5 days every 3 weeks.

Dacarbazine can be administered as short-term infusion (over 20 – 30 minutes).

It is also possible to give 850 mg/m$^2$ 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/$m^2$ body surface area intravenously every 15 days in combination with doxorubicin, bleomycin and vinblastine (ABVD regimen).

*Soft tissue sarcoma*
For adult soft tissue sarcoma, dacarbazine is given in daily doses of 250 mg/$m^2$ body surface area intravenously (days 1 – 5) in combination with doxorubicin every 3 weeks (ADIC regimen).

*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 soft tissue sarcoma, the duration of treatment depends on the efficacy and tolerability in the individual patient.

*Special patient 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.

Paediatric population:
The safety and efficacy of Dacarbazine Lipomed in children and adolescents have not yet been established.

Method of administration
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 during administration to avoid paravenous application since this could cause local pain and tissue damage.

If paravenous application occurs, the administration should be discontinued immediately and any remaining portion of the dose should be introduced into another vein.

*Rate of infusion*
Doses ranging from 200 to 850 mg/$m^2$ body surface area should be administered as an intravenous infusion over 20 – 30 minutes.

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

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6. Reconstituted solutions are clear and pale yellow. Diluted solutions for infusion are clear and almost colourless.

**4.3 Contraindications**

Dacarbazine Lipomed is contraindicated in the following cases:

- Hypersensitivity to the active substance dacarbazine or to any of the excipients listed in section 6.1,
- Pregnant or breastfeeding women,
- Leukopenia and/or thrombocytopenia,
- Severe liver or kidney disease,

- In combination with yellow fever vaccine (see section 4.5).

**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, having the facilities for the necessary regular monitoring of clinical, biochemical and haematological effects during and after therapy.

If symptoms of 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 regular monitoring of liver size, function and blood counts (especially eosinophils) is particularly important. In single cases of suspected veno-occlusive disease, 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 red and white blood cells and of platelets. Haematopoetic toxicity may warrant temporary suspension or cessation of therapy.

Paravenous injection may result in tissue damage and severe pain.

Concomitant use of phenytoin should be avoided since there is a risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption (see section 4.5).

Furthermore, dacarbazine is a moderate immunosuppressive agent. Administration of live vaccines (live-attenuated) in patients immunocompromised by chemotherapeutic agents such as dacarbazine may result in serious and potentially fatal infections. Vaccination with a live vaccine should be avoided in patients receiving dacarbazine. Inactivated vaccines may be used where they exist.

Hepatotoxic drugs and alcohol are contraindicated during chemotherapy.

Contraceptive measures:
Men are advised to take contraceptive measures during and for 6 months after cessation of therapy (see section 4.6).

*Paediatric population:*
Dacarbazine is not recommended for use in children and adolescents 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 interactions**

Concomitant use of yellow fever vaccine is contraindicated because of the risk of fatal systemic disease (see section 4.3).

Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with oral anticoagulants, to increase the frequency of the INR monitoring.

Concomitant use of phenytoin should be avoided since there is a risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption (see section 4.4).

Concomitant use of live-attenuated vaccines should be avoided since there is a risk of systemic, possibly fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. It is recommended using an inactivated vaccine where this exists (poliomyelitis) (see also section 4.4).

Concomitant use of cyclosporin (and by extrapolation tacrolimus) should be carefully considered since use of these agents causes excessive immunosuppression with the risk of lymphoproliferation.

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

Myelotoxic interactions with other treatment modalities having adverse effects on the bone marrow (particularly cytostatic agents, irradiation) are possible.

Studies to investigate potential phenotypic metabolism have not been undertaken. However, 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 Fertility, pregnancy and lactation**

Pregnancy and breast-feeding:
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. For this reason, dacarbazine must not be used during pregnancy and while breast-feeding (see also sections 4.3 and 4.4). It is not known if dacarbazine crosses the placenta or distributes into milk.

Women of child bearing potential:
Women of child bearing age must use effective methods of contraception.

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

**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)

The most commonly reported adverse drug reactions 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.

| System Organ Class | Frequencies | | |
|---|---|---|---|
| | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) |
| Infections and | | Infections | |

| | | | |
|---|---|---|---|
| infestations | | | |
| Blood and lymphatic system disorders | Anaemia, leukopenia, thrombocytopenia, bone marrow suppression | | Pancytopenia, agranulocytosis |
| Immune system disorders | | | Anaphylactic reactions, hypersensitivity reactions |
| Nervous system disorders | | | Headaches, confusion, lethargy, convulsions, facial paraesthesia |
| Eye disorders | | Blurred vision | Impaired vision |
| Vascular disorders | | | Facial flushing |
| Gastrointestinal disorders | Anorexia, nausea, vomiting | | Diarrhoea |
| Hepatobiliary disorders | | Hepatotoxicity | Hepatic necrosis due to veno-occlusive disease, Budd-Chiari syndrome with potential fatal outcome |
| Renal and urinary disorders | | | Impaired renal function with increased blood creatinine and increased blood urea |
| Skin and subcutaneous tissue disorders | | Alopecia, hyperpigmentation, photosensitivity, transient rash | Erythema, maculopapular exanthema, urticaria |
| General disorders and administration site disorders | | Flu-like symptoms, malaise | Application site irritation |
| Investigations | | | Elevation of liver enzymes, increased transaminases (AST, ALT), increased alkaline phosphatase, increased lactate dehydrogenase (LDH) |

Gastrointestinal disturbances such as anorexia, nausea and vomiting are common and severe. In rare cases, diarrhoea has been observed.

Changes in blood counts often observed (anaemia, leukopenia, thrombocytopenia) are dose-dependent and delayed, with the nadirs often occurring only 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 chemotherapy 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, regular monitoring of liver size, function and blood counts (especially eosinophils) is particularly important. In single cases of suspected veno-occlusive disease, 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 sections 4.2 and 4.4).

Application site reactions such as irritation of the vein 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 obligatorily 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 administration.

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 application is expected to cause local pain and necrosis.

Reporting of 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

**4.9 Overdose**

Severe bone marrow toxicity and even bone marrow aplasia can be expected as consequences of an overdose and the onset can be delayed by up to 2 weeks. The time to occurrence of nadirs of leucocytes and thrombocytes can be 4 weeks. Even if an overdose is only suspected, long-term, careful haematologic monitoring is therefore essential.

Hypotensive episodes have been observed with high doses of dacarbazine (> 850 mg/m$^2$). If hypotension is observed, supportive treatment is recommended, for example hydration with 500 ml of 0.9% sodium chloride solution.

Since there is no known antidote available, utmost care has to be taken at each administration to avoid an overdose.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Alkylating agents; ATC code: L01AX04.

Dacarbazine is a cytostatic agent. The anti-neoplastic 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 be effective 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 effects of the drug.

**5.2 Pharmacokinetic properties**

After intravenous administration dacarbazine is quickly distributed from the intravascular space into tissue. Plasma protein binding is 5%. Dacarbazine's kinetics in the plasma are biphasic. The initial (distribution) half-life is only 20 minutes, the terminal half-life is 0.5 to 3.5 hours.

Dacarbazine crosses the blood-brain barrier to a limited extent; concentrations in the cerebrospinal fluid are reported to be about 14% of plasma concentrations.

Dacarbazine is inactive until metabolised in the liver by cytochrome 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 metabolised mainly in the liver by hydroxylation and demethylation, approx. 20% to 50% is excreted unmodified by the kidney via renal tubular secretion.

**5.3 Preclinical safety data**

Because of its pharmacological 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 and mannitol.

### 6.2 Incompatibilities

Attention should be paid to the chemical incompatibility of dacarbazine solution with heparin, hydrocortisone, L-cysteine and sodium hydrogen carbonate.

In the absence of compatibility studies, Dacarbazine Lipomed 500 mg must not be mixed with other medicinal products.

### 6.3 Shelf life

3 years.

Shelf life of the reconstituted solution
Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature and protected from light and for 5 days at 2 to 8°C and protected from light. From a microbiological point of view, the reconstituted solution should be used immediately.
If the reconstituted solution is not used immediately, the duration and conditions of storage are the responsibility of the user. The reconstituted solution should not be stored for 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 of the diluted solution for infusion
Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature and protected from light and for 5 days at 2 to 8°C and protected from light. From a microbiological point of view, the diluted solution for infusion should be used immediately.
If the diluted solution for infusion is not used immediately, the duration and conditions of storage are the responsibility of the user. The diluted solution for infusion should not be stored for 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.

From a microbiological point of view it is recommended not to exceed a total storage time of 24 hours after opening of the product.

### 6.4 Special precautions for storage

Do not store above 25°C, keep the vial in the outer carton in order to protect from light.

Reconstituted solutions should also be protected from light.

For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Dacarbazine Lipomed 500 mg is supplied as sterile powder for solution for infusion in single-dose brown injection vials (hydrolytical class I) closed with bromobutyl rubber lyophilisation stoppers. Vials containing Dacarbazine Lipomed 500 mg are aluminium crimped with grey flip-off caps. Dacarbazine Lipomed 500 mg is packed in cartons containing 1 vial each.

### 6.6 Special precautions for disposal and other handling

*Recommendations for the safe handling*
Dacarbazine is an anti-neoplastic agent. Before commencing, local cytotoxic guidelines should be referred to. Dacarbazine solutions should only be prepared by trained staff. 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 of the work, 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 working area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin or stored in a sealed container 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 aluminum foil.

Under aseptic conditions, the contents of one vial of Dacarbazine Lipomed 500 mg is first dissolved with 50 ml of water for injections. The density of the solution is 1.007 g/ml. The resulting solution has to be further diluted in 200 – 300 ml isotonic sodium chloride solution or glucose 5%. The infusion solution ready for administration (1.4 – 2.0 mg/ml) should be given intravenously within 20 – 30 minutes.

Dacarbazine Lipomed 500 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. This is also applicable for solutions where the visual appearance of the product has changed.

Reconstituted solutions are clear and pale yellow. Diluted solutions for infusion are clear and almost colourless.

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

**7 MARKETING AUTHORISATION HOLDER**

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

**8 MARKETING AUTHORISATION NUMBER**

PA1760/001/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 18th August 2017

**10 DATE OF REVISION OF THE TEXT**

April 2021