Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dacarbazine Lipomed 200 mg powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg dacarbazine (as dacarbazine citrate in-situ formation).

After reconstitution, Dacarbazine Lipomed 200 mg contains 10 mg/ml dacarbazine (see section 6.6).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dacarbazine Lipomed is indicated for the treatment of patients with metastatic malignant melanoma.

Further indications for dacarbazine as part of a combination chemotherapy are:

- Advanced Hodgkin's disease.
- Advanced adult soft tissue sarcomas (except for mesothelioma and Kaposi sarcomas).

4.2 Posology and method of administration

Dacarbazine Lipomed should be confined to physicians experienced in oncology or haematology 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 during the 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.

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

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

<u>Malignant melanoma</u>
Dacarbazine can be used as single agent in doses of 200 to 250 mg/m^2 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/m^2 body surface area on day 1 and then once every 3 weeks as intravenous infusion.

<u>Hodgkin's disease</u>
Dacarbazine is administered in a daily dose of 375 mg/m^2 body surface area i.v. every 15 days in combination with doxorubicin, bleomycin and vinblastin (ABVD regimen).

Soft tissue sarcoma

For adult soft tissue sarcomas, dacarbazine is given in daily doses of 250 mg/m^2 body surface area i.v. (days 1-5) in combination with doxorubicin every 3 weeks (ADIC 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.

As severe gastrointestinal and haematological disturbances can occur, a very careful benefit-risk analysis must be carried out before each treatment with Dacarbazine Lipomed.

Therapy duration

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

Rate of administration of the injection/infusion

Doses of up to 200 mg/m^2 may be given as a slow intravenous injection over approximately 1 minute. Larger doses (ranging from 200 to 850 mg/m^2) should be administered as an intravenous infusion over 15 to 30 minutes.

It is recommended testing first the patency of the vein with a 5 to 10 ml flush of isotonic 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 injections and without further dilution with isotonic sodium chloride solution or glucose 5%, Dacarbazine Lipomed 200 preparations are hypo-osmolar (ca. 100 mOsmol/kg) and should therefore be given by slow intravenous injection, e.g., over 1 minute and not as an i.v. bolus injection over a few seconds.

Special populations

Patients with renal/hepatic 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 currently be given.

Elderly patients

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

Children

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

For instructions for preparation and reconstitution, see section 6.6.

4.3 Contraindications

Dacarbazine Lipomed is contraindicated in the following cases:
- Hypersensitivity to dacarbazine or to any of the excipients,
- 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 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, therapy must be immediately discontinued.
If veno-occlusive disease of the liver occurs, further therapy with dacarbazine is contraindicated.
Note: The responsible physician must be aware during therapy of the possibility of a rare, severe complication of liver necrosis that occurs as a result of occlusion of the intrahepatic veins. Regular monitoring of liver size, function and blood counts (especially eosinophils) is of particular importance. In single suspected cases of veno-occlusive disease, early treatment with high dose corticosteroids (for example hydrocortisone 300 mg/day), with or without fibrinolytic substances such as heparin or tissue plasminogen activator, was successful (also see section 4.8).

Long-term therapy can cause cumulative bone marrow toxicity. Possible suppression of the bone marrow requires careful monitoring of the red and white blood cells and platelets. Haematopoietic toxicity may warrant temporary discontinuation or cessation of therapy.

Extravasation can 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).

Immunosuppressant effects/increased susceptibility to infections
Dacarbazine is a moderate immunosuppressive agent. Administration of live vaccines (live-attenuated) in patients immunocompromised by chemotherapeutic agents including dacarbazine, may result in serious or 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 therapy and for 6 months after cessation of therapy.

Administration of dacarbazine to children
No special recommendations for the use of dacarbazine in the paediatric age group can be given 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 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. Dacarbazine should be administered over one week after fotemustine administration.

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 a possible phenotypic metabolism have not been undertaken. The 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 must be taken into account if other medicinal products are co-administered with dacarbazine that are metabolised by the same hepatic enzymes.

Dacarbazine can enhance the effects of methoxypsoralen because of photosensitisation.

4.6 Fertility, pregnancy and lactation

Dacarbazine has been shown to be mutagenic, teratogenic and carcinogenic in animals. It must therefore be assumed that there is an increased risk of teratogenic effects in humans. For this reason, dacarbazine must not be used during pregnancy and while breastfeeding (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 age
Women of child bearing age must use effective methods of contraception.

Men treated with dacarbazine
Men are advised to take contraceptive measures during therapy 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 and also 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)

Blood and lymphatic system disorders	Common Anaemia, leukopenia, thrombocytopenia, bone marrow suppression Rare Pancytopenia, agranulocytosis
Immune system disorders	Rare Anaphylaxis, hypersensitivity reactions
Psychiatric disorders	Uncommon Confusion
Nervous system disorders	Rare Headache, lethargy, convulsions, facial paraesthesia
Eye disorders	Uncommon Blurred vision Rare

	Impaired vision
Vascular disorders	Uncommon Facial flushing
Gastrointestinal disorders	Common Anorexia, nausea, vomiting Rare Diarrhoea
Hepatobiliary disorders	Uncommon Increased transaminases (AST, ALT), increased alkaline phosphatase, increased lactate dehydrogenase (LDH). Hepatotoxicity, hepatic vein thrombosis, hepatic necrosis, Budd-Chiari syndrome with potential fatal outcome.
Skin and subcutaneous tissue disorders	Uncommon Alopecia, hyperpigmentation, photosensitivity, transient rash Rare Erythema, maculopapular exanthema, urticaria
Renal and urinary disorders	Uncommon Impaired renal function with increased blood creatinine and increased blood urea
General disorders and administration site conditions	Uncommon Flu-like symptoms, malaise Rare Injection site irritation

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 (anaemia, 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 muscle pain are occasionally observed during or often only days after dacarbazine administration. These disturbances may recur at the next infusion.

Elevation of liver enzymes (e.g. transaminases (AST, ALT), alkaline phosphatase, lactate dehydrogenase (LDH)) has been observed uncommonly.

Uncommonly liver necrosis due to occlusion of intrahepatic veins (veno-occlusive disease) has been observed after administration of dacarbazine as a monotherapy or combined chemotherapy. Normally 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 outcomes have been described, frequent monitoring of liver size, function and blood counts (especially eosinophils) is particularly important during treatment. 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 also sections 4.2 and 4.4).

Local disorders at the application site such as vein irritation and some of the systemic adverse reactions are thought to result from the formation of photo-degradation products. Local pain and necrosis is to be expected following inadvertent extravasation.

Impaired renal function with increased blood levels of substances which have to be excreted in the urine is uncommon.

Central nervous disorders such as headaches, impaired vision, confusion, lethargy and convulsions rarely may occur. Facial paraesthesia and flushing may occur shortly after the injection.

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

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 the national reporting system:

IMB Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.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 essential.

There is no known antidote available and therefore special care has to be taken at each administration to avoid an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other 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 further 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 effects.

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; CSF concentrations 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 both 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 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 (E 421)

6.2 Incompatibilities

It should be noted that dacarbazine solution is chemically incompatible with heparin, hydrocortisone, L-cysteine and sodium hydrogen carbonate.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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 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.
Store in the original package in order to protect from light.

Reconstituted solutions should also be protected from light.
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-dose brown vials (Type I Ph.Eur.) closed with bromobutyl rubber stoppers and packed in cartons of 10 vials.

6.6 Special precautions for disposal and other handling

Recommendations for safe handling
Dacarbazine is an antineoplastic agent. Before preparing a solution, local cytotoxic guidelines should be referred to regarding handling of cytotoxic agents.
Dacarbazine should only be opened 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 the solution for administration should be carried out in a designated handling area, working over a washable tray or disposable plastic-backed absorbent paper.
It is recommended that suitable eye protection, disposable gloves, face mask and a disposable apron are worn. Syringes and infusion sets should be assembled carefully to avoid leaks (use of Luer lock fittings is recommended).

Once completed, any exposed surfaces should be thoroughly cleaned and the hands and face washed.

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

Preparation and administration of the solution for injection or infusion
Dacarbazin Lipomed 200 mg powder for solution for injection or infusion should be reconstituted with 19.7 ml of water for injections. The resulting solution contains 10 mg/ml dacarbazine and has a pH of 3.0 to 4.0.

For preparation of infusion solutions, the reconstituted solution should be diluted with 200 ml glucose 5% or sodium chloride solution 0.9%. The resulting solution contains 1.0 mg/ml.

The solutions prepared by reconstitution or by reconstitution and dilution must be clear and free from visible particles.

All prepared solutions must be protected from light; the administration should also take place without exposure to daylight.

Any unused product or waste material should be disposed off in accordance with local requirements.

For single use only.

7 MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil/Rhein
Germany

8 MARKETING AUTHORISATION NUMBER

PA1760/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th July 2012
Date of last renewal: 1st February 2013

10 DATE OF REVISION OF THE TEXT

July 2019