SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dacarbazine medac 100 mg, powder for solution for injection/infusion
Dacarbazine medac 200 mg, powder for solution for injection/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 100 mg contains 100 mg dacarbazine (as dacarbazine citrate, formed in situ).

After reconstitution Dacarbazine medac 100 mg contains 10 mg/ml dacarbazine.

Each single-dose vial of Dacarbazine medac 200 mg contains 200 mg dacarbazine (as dacarbazine citrate, formed in situ). After reconstitution Dacarbazine medac 200 mg contains 10 mg/ml dacarbazine.

Each single-dose vial of Dacarbazine medac 500 mg contains 500 mg dacarbazine (as dacarbazine citrate, formed in situ). After reconstitution and final dilution Dacarbazine medac 500 mg contains 1.4 – 2.0 mg/ml dacarbazine.

Each single-dose vial of Dacarbazine medac 1000 mg contains 1,000 mg dacarbazine (as dacarbazine citrate, formed in situ). After reconstitution and final dilution Dacarbazine medac 1000 mg contains 2.8 – 4.0 mg/ml dacarbazine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dacarbazine medac 100 mg (200 mg): Powder for solution for injection/infusion.
Dacarbazine medac 500 mg (1000 mg): Powder for solution for infusion.
Dacarbazine medac is a white or pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dacarbazine is indicated for the treatment of patients with metastasised 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

Posology

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

The following regimes may 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/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).

Adult soft-tissue sarcoma
For adult soft tissue sarcomas dacarbazine is given in daily doses of 250 mg/m² 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.
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.

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 metastasised malignant melanoma and in advanced tissue sarcoma, the duration of treatment depends on the efficacy and tolerability in the individual patient.

Renal and/or hepatic impairment
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
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 in children/adolescents aged < 15 years have not yet been established. No special recommendations for the use of dacarbazine in the paediatric age group can be given until further data become available.

Method of administration

Precautions to be taken before handling or administering the medicinal product
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 when administering 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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

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 0.9 % sodium chloride or 5 % glucose solution for infusion. The same solutions should be used after infusion to flush any remaining medicinal product from the tubing.

After reconstitution with water for injections without further dilution with 0.9 % sodium chloride or 5 % glucose solution for infusion, dacarbazine 100 mg and 200 mg preparations are hypo-osmolar (ca. 100 mOsmol/kg) and should therefore be given by slow intravenous injection e.g. over 1 minute rather than rapid intravenous bolus over a few seconds.

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.

Fotemustine and dacarbazine should not be used concomitantly (see section 4.5).

Hepatotoxic medicinal products and alcohol should be avoided during chemotherapy.

Women of childbearing potential/contraception in men and women
Due to the genotoxic potential of dacarbazine (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with Dacarbazine medac 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 medac and for 3 months following completion of treatment.
Patients considering pregnancy should seek genetic counselling after the period of contraceptive use (see section 4.6).

Paediatric population
Dacarbazine is not recommended for use in the paediatric age group until further data become available.

For precautions on handling, please see section 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 interindividual 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 lymphoproliferation.

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.

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 medac is contraindicated during pregnancy (see section 4.3).
Women of childbearing potential/contraception in men and women
Due to the genotoxic potential of dacarbazine (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with Dacarbazine medac 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 medac and for 3 months following completion of treatment.

Breastfeeding
Dacarbazine medac is contraindicated during breast-feeding (see section 4.3).

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

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
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 (LDH) 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 sections 4.2 and 4.4).

Application site irritations and some of the systemic adverse reactions are thought to result from formation of photodegradation 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 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 listed in Appendix V.

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 overdose is only suspected, long-term careful haematologic 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alkylating agents, ATC code: L01AX04.

Mechanism of action
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, anhydrous and mannitol.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

Shelf life of the reconstituted solution of Dacarbazine medac 100 mg (200 mg, 500 mg, 1000 mg):
Chemical and physical in-use stability has been demonstrated for 48 hours at 2 – 8 °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 – 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 100 mg (200 mg, 500 mg, 1000 mg):
Chemical and physical in-use stability has been demonstrated for 2 hours at 25 °C for the reconstituted and further diluted solution in polyethylene containers and for 24 hours at 2 – 8 °C protected from light in polyethylene containers as well as in glass bottles. From a microbiological point of view, 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 the outer carton in order to protect from light. Reconstituted solutions should also be protected from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Dacarbazine medac 100 mg (200 mg) is supplied as a sterile powder for solution for injection/infusion in single-dose vials made of amber glass (Type I, Ph.Eur.) and closed with butyl rubber stoppers. Each carton of Dacarbazine medac 100 mg (200 mg) contains 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 (1000 mg) contains one vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Recommendations for safe handling
Dacarbazine is an antineoplastic agent and should be handled according to standard procedures for cytostatics that have mutagenic, carcinogenic and teratogenic effects. 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 medicinal products 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 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 100 mg:
Aseptically transfer 10 ml of water for injections into the vial and shake until a solution is obtained. This freshly prepared solution, containing10 mg/ml of dacarbazine (density of the solution: $\rho = 1.007$ g/ml) is administered as a slow injection.

For preparation of Dacarbazine medac 100 mg for i.v. infusion the freshly prepared solution is further diluted with 200 – 300 ml 0.9 % sodium chloride or 5 % glucose solution for infusion. This solution is given as a short-term infusion over a period between 15 – 30 minutes.

b) Preparation of Dacarbazine medac 200 mg:
Aseptically transfer 20 ml of water for injections into the vial and shake until a solution is obtained. This freshly prepared solution, containing10 mg/ml of dacarbazine, (density of the solution: $\rho = 1.007$ g/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 0.9 % sodium chloride or 5 % glucose solution for infusion. This solution is given as a short-term infusion over a period between 15 – 30 minutes.

c) Preparation of Dacarbazine medac 500 mg:
Aseptically transfer 50 ml water for injections into the vial and shake until a solution is obtained. The resulting solution, containing 10 mg/ml of dacarbazine (density of solution: $\rho = 1.007$ g/ml) has to be further diluted with 200 – 300 ml 0.9 % sodium chloride or 5 % glucose solution for infusion. The obtained solution for infusion, containing 1.4 – 2.0 mg/ml of dacarbazine, is ready for i. v. infusion and should be given over a period between 20 – 30 minutes.

d) Preparation of Dacarbazine medac 1000 mg:
Aseptically transfer 50 ml water for injections into the vial and shake until a solution is obtained. The resulting solution, containing 20 mg/ml of dacarbazine (densitiy of solution: $\rho = 1.015$ g/ml) has to be further diluted with 200 – 300 ml 0.9 % sodium chloride or 5 % glucose solution for infusion. The obtained solution for infusion, containing 2.8 – 4.0 mg/ml of dacarbazine, is ready for i. v. infusion and should be given over a period between 20 – 30 minutes.

Dacarbazine medac 100 mg (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 solutions where the visual appearance has changed should be discarded.

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

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

08/2023