Professional information for DARAZ 200

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DARAZ 200 powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 200 mg dacarbazine.

After reconstitution DARAZ 200 contains 10 mg/mL dacarbazine.

Excipients with known effect:

Contains mannitol.

Sugar free.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

White to pale yellow, freeze-dried cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Metastatic malignant melanoma.
- Metastatic sarcoma in combination with other chemotherapeutic medicines.
- Hodgkin’s disease.

- Other malignant diseases in combination with other cytotoxic medicines, including carcinomas of colon, ovary, breast and lung and testicular teratoma.

4.2 Posology and method of administration

Posology

The following schedule is recommended:

2 - 4,5 mg/kg/day for 10 days which may be repeated at 3 week intervals. It has been found that DARAZ 200 may be as efficacious at the lower dosage as at the higher dosage. Combinations of cancer chemotherapeutic medicines have often shown an improved response over the use of a single medicine.

If desired, the reconstituted solution may be further diluted with 150 - 250 mL of 5 % dextrose for injection of normal saline for injection and administered by intravenous infusion over a period of 15 - 30 minutes.

Method of administration

DARAZ 200 is injected as a slow intravenous injection. Injection may be completed in approximately one minute.

For instructions on reconstitution of DARAZ 200 before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to dacarbazine or to any of the excipients of DARAZ 200 (see section 6.1).
- Pregnancy and lactation.
- Leukopenia and thrombocytopenia.
- Severe liver or kidney diseases.

4.4 Special warnings and precautions for use

General

It is recommended that DARAZ 200 should only be administered under the supervision of a medical practitioner specialised in oncology who has the facilities for regular monitoring of clinical, biochemical and haematological effects, during and after therapy.

Liver or kidney disorder or hypersensitivity reaction

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 DARAZ 200 is contraindicated (see section 4.3).

Liver necrosis

Note: The responsible medical practitioner 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 medicines like heparin or tissue plasminogen activator was successful (see section 4.8).

Bone marrow toxicity

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.

Intravenous (IV) administration

Extravasation of DARAZ 200 during IV administration may result in tissue damage and severe pain.

In combination with phenytoin

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).

Immunisation with live vaccines

DARAZ 200 is a moderate immunosuppressive medicine. Administration of live vaccines to patients who are immunocompromised as a result of treatment with chemotherapeutic medicines, such as DARAZ 200, can cause serious and potentially fatal infections. Immunisation with live vaccines should therefore be avoided during DARAZ 200 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.

In combination with fotemustine

Concomitant use of fotemustine can cause acute pulmonary toxicity (adult respiratory distress syndrome), which may lead to a fatal outcome. Fotemustine and DARAZ 200 should not be used concomitantly (see section 4.5).

Hepatotoxic medicines and alcohol

Hepatotoxic medicines 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

DARAZ 200 is not recommended for use in the paediatric age group until further data become available.

4.5 Interaction with other medicines and other forms of interaction

Cytostatic medicines or irradiation

In case of previous or concomitant treatment having adverse effects on the bone marrow (particularly cytostatic medicines or irradiation) myelotoxic interactions are possible.

Medicines metabolised by cytochrome P450

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. DARAZ 200 is metabolised by cytochrome P450 (CYP1A1, CYP1A2 and CYP2E1). This has to be taken into account if other medicines are co-administered which are metabolised by the same hepatic enzymes.

Methoxypsoralen

DARAZ 200 can enhance the effects of methoxypsoralen because of photosensitisation.

Immunisation with live vaccines

Immunisation with live vaccines should be avoided during therapy with DARAZ 200 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 section 4.4).

Oral anticoagulants

Risk of thrombosis is increased in malignant diseases; therefore, the use of concomitant anticoagulation is common. If the patient is to receive oral anticoagulants, the frequency of international normalised ratio (INR) monitoring must be increased due to large interindividual

variability in coagulation and due to possible interaction between anticoagulants and cytostatic medicines.

Phenytoin

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).

Ciclosporin and tacrolimus

Concomitant use of ciclosporin (and in some cases tacrolimus) must be considered carefully because these medicines may cause excessive immunosuppression and lymphoproliferation.

Fotemustine

Concomitant use of fotemustine can cause acute pulmonary toxicity (adult respiratory distress syndrome). Fotemustine and DARAZ 200 should not be used concomitantly (see section 4.4).

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should use effective contraception during DARAZ 200 treatment. Men are advised to take contraceptive measures during and for 6 months after cessation of therapy.

Pregnancy

Dacarbazine, as in DARAZ 200, is contraindicated in pregnancy. It 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 (see section 4.3 and 4.4).

Lactation

DARAZ 200 is contraindicated during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

DARAZ 200 may influence the ability to drive or operate machines because of its central nervous system side effects or because of side effects, such as nausea and vomiting. Caution is advised before performing tasks that require attention, until the effects of DARAZ 200 are known.

4.8 Undesirable effects

The most frequent undesirable eeffects are gastrointestinal disorders (anorexia, nausea and vomiting) and blood and lymphatic system disorders, such as anaema, leukopenia and thrombocytopenia. The latter are dose-dependant and delayed, with the nadirs often only occuring after 3 to 4 weeks.

Infections and infestations:

Less frequent: infections

Blood and the lymphatic system disorders:

Frequent: anaemia, leukopenia, thrombocytopenia

Less frequent: pancytopenia, agranulocytosis

Immune system disorders:

Less frequent: anaphylactic reactions

Nervous system disorders:

Less frequent: headaches, confusion, lethargy, convulsions, facial paraesthesia

Eye disorders:

Less frequent: impaired vision

Vascular disorders:

Less frequent: facial flushing

Gastrointestinal disorders:

Frequent: anorexia, nausea, vomiting

Less frequent: diarrhoea

Hepatobiliary disorders:

Less frequent: hepatic necrosis due to veno-occlusive disease (VOD) of the liver, Budd-Chiari syndrome (with potentially fatal outcome)

Skin and subcutaneous tissue disorders:

Less frequent: alopecia, hyperpigmentation, photosensitivity, erythema, maculopapular exanthema, urticaria

Renal and urinary disorders:

Less frequent: impaired renal function

General disorders and administration site conditions:

Less frequent: flu-like symptoms, application site irritation

Investigations:

Less frequent: increased hepatic enzymes (e.g. alkaline phosphatase, ASAT, ALAT), increased blood lactate dehydrogenase (LDH), increased blood creatinine, increased blood urea

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.

DARAZ 200 may cause diarrhoea. Some helpful suggestions include restricting the patient's oral intake of fluids and food for 4 – 6 hours prior to treatment. The rapid toleration of these symptoms suggest that a central nervous system mechanism may be involved and usually these symptoms subside after the first 1 or 2 days. Intractable nausea and vomiting have necessitated discontinuance of DARAZ 200 therapy.

Flu-like symptoms with exhaustion, chills, fever and muscular pain are occasionally observed during or often only days after DARAZ 200 administration. These disturbances may recur with the next infusion.

Toxicity is enhanced when kidney malfunction occurs. Alopecia has been noted, as has facial flushing and facial paraesthesias.

Rarely liver necrosis due to occlusion of intrahepatic veins (veno-occlusive disease of the liver) has been observed after administration of DARAZ 200 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 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 DARAZ 200 is important. It allows continued monitoring of the benefit/risk balance of DARAZ 200. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

The primary anticipated complications of overdose are severe bone marrow suppression and 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 haematological monitoring is essential.

Treatment

There is no known antidote for dacarbazine overdose, treatment is therefore supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic Agents

Pharmacotherapeutic group: Alkylating agents

ATC code: L01AX04

Dacarbazine is a cytostatic medicine. 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 by acting as a purine analogue. 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 dacarbazine.

5.2 Pharmacokinetic properties

Distribution:

After intravenous administration dacarbazine is 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 cytochrome P450 to form the reactive *N*-demethylated species HMMTIC (5-[3-hydroxymethyl-3-methyl-1-triazeno]-imidazole-4-carboxamide) and MTIC (5-[3-methyl-1-triazeno]-imidazole-4-carboxamide). 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; approximately 20 – 50 % of dacarbazine 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 (pH adjuster) (E330);

D-mannitol (E421);

water for injection.

6.2 Incompatibilities

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

6.3 Shelf life

36 months.

Before reconstitution:

Store between 2 °C and 8 °C.

After reconstitution:

From a microbiological point of view, DARAZ 200 should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

After reconstitution (with 19,7 mL *sterile water for injection):*

Store between 2 °C and 8 °C for up to 72 hours and at or below

25 °C for up to 8 hours.

After dilution of the reconstituted solution (with 150 – 250 mL *5 % dextrose or 0,9 % sodium chloride for injection):*

Store between 2 °C and 8 °C for up to 24 hours and at or below 25 °C for up to 8 hours.

6.4 Special precautions for storage

Protect from light (before and after reconstitution).

ALL RECONSTITUTED SOLUTIONS MUST BE PROTECTED FROM LIGHT AND USED WITHIN ONE HOUR.

6.5 Nature and contents of container

20 mL amber type 1 glass vial closed with a grey chlorobutyl rubber stopper and sealed with an aluminium seal and a red flip-off cap, packed in an outer carton.

Pack size: 10 vials.

6.6 Special precautions for disposal and other handling

DARAZ 200 vials are reconstituted with 19,7 mL of water for injection. The resulting solution contains an equivalent of 10 mg/mL of dacarbazine. After the solution has been prepared, the calculated dose of the resulting solution is drawn into a syringe and injected intravenously.

Recommendations for safe handling:

- DARAZ 200 is an antineoplastic medicine and should be handled accroding to standard procedures for cytostatics that have mutageic, carcinogenic and teratogenic effects.
- DARAZ 200 should only be opened by trained health care providers and as with all cytotoxic medicines, precautions should be taken to avoid exposing the healthcare workers. Handling of cytotoxic medicines 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, healthcare workers should put on gloves, face masks, eye-protection and disposable aprons 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:

DARAZ 200 solutions are prepared immediately before use.

DARAZ 200 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, e.g. in UV-resistant foils.

Aseptically transfer 19,7 mL of water for injections into the vial and shake until a solution is obtained. This freshly prepared solution, containing 10 mg/mL of DARAZ 200 (density of the solution: ρ = 1,007 g/mL), is administered as a slow injection.

For preparation of DARAZ 200 IV infusion the freshly prepared solution is further diluted with 150 – 200 mL 0,9 % sodium chloride for injection or 5 % dextrose infusion solution. This solution is given as a short-term infusion over a period between 15 to 30 minutes.

DARAZ 200 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, as well as solutions where the visual appearance of DARAZ 200 has changed.

Any unused DARAZ 200 or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ando Pharma (Pty) Ltd

73 Keurboom Crescent

Plattekloof

Cape Town 7500

8. REGISTRATION NUMBER

54/26/0028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 December 2022

10. DATE OF REVISION OF THE TEXT