IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0437/040/002
Case No: 2072705

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

HOSPIRA UK Ltd

Queensway, **Royal Leamington Spa**, **Warwickshire CV31 3RW**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Dacarbazine 200mg Powder for Solution for Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/01/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dacarbazine 200mg Powder for Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200mg of dacarbazine.

When reconstituted as directed in sections 4.2 and 6.6, each ml of medicinal solution contains 10mg of dacarbazine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

White or very pale yellow powder or plug.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Metastatic malignant melanoma
2. Solid tumours
3. Hodgkin's disease

In addition, dacarbazine has been shown, when used in combination with other agents, to be of use in the treatment of other malignant diseases.

4.2 Posology and method of administration

Dosage and Administration

Dosage:

Standard dose: The following dosage schedules are recommended:

1. 2.0-4.5mg/kg/day for 10 days, which may be repeated at 4 week intervals.
2. 250mg/m^2/day for 5 days which may be repeated at three week intervals.
3. A further alternative is to administer the total schedule dose on the first day.

Other schedules may be used at the discretion of the prescribing physician.

Children:

The dosage for children is calculated on the mg/kg or mg/m^2 basis as per the standard dosage. There is no induction that children require a different dosage range **or** metabolise or react differently to the drug.

Geriatric:

As for paediatric use.

With Impaired Hepatic Function

As the drug partly undergoes metabolism in the liver, impairment of liver function is likely to necessitate a variation in dosage.

With Impaired Renal Function

As the drug is excreted 50% unchanged in the urine by tubular secretion, impairment of renal function is likely to necessitate a change in dosage.

Administration

Administration is by the IV route only.

Dacarbazine 100mg and 200mg vials should be reconstituted with 9.9 ml and 19.7 ml respectively, with Water for Injections BP. The resulting solutions contain the equivalent of 10mg/ml of dacarbazine and have a pH of 3 to 4. The resultant solution should be injected intravenously over one to two minutes.

If desired the reconstituted solution can be further diluted with 125-250ml of Dextrose Injection BP 5% or Sodium Chloride Injection BP 0.9% and administered by intravenous infusion over 15-30 minutes.

4.3 Contraindications

Dacarbazine is contraindicated in patients who have demonstrated a hypersensitivity to Dacarbazine in the past.

Dacarbazine should not be administered to patients who are pregnant or may become pregnant or breast feeding mothers.

Patients who have previously had severe myelosuppression.

4.4 Special warnings and precautions for use

Warnings
Haemopoietic depression is the most common toxic side-effect of dacarbazine and involves primarily the leucocytes and platelets, although mild anaemia may sometimes occur. Leucopenia and thrombocytopenia may be severe enough to cause death. Possible bone marrow depression requires careful monitoring of white blood cells, red blood cells and platelet levels. Such toxicity may necessitate temporary suspension or cessation of therapy.

Hepatic toxicity, accompanied by hepatic vein thrombosis and hepatocellular necrosis resulting in death, have been reported. The incidence of such reactions has been low. This toxicity has been observed mostly when dacarbazine has been administered concomitantly with other anti-neoplastic drugs; however, it has also been reported in some patients treated with dacarbazine alone.

Precautions
The drug can produce severe and possibly fatal, haematologic or hepatic toxicity and severe GI reactions and should be administered to patients preferably within the hospital setting, where they can be observed frequently during and after therapy, particularly with regards to the haemopoietic toxicity.

It is recommended that dacarbazine be administered under the supervision of a specialist oncology service having laboratory facilities for monitoring of clinical, biochemical and haemetabological effects during and after therapy.

Restriction of food intake for 4-6 hours prior to treatment may reduce the severity of the nausea and vomiting which occurs in most patients particularly during the first two days of treatment. Administration of an anti-emetic may also reduce the severity of these effects.

Impairment of renal and liver function: See dosage in impaired renal and liver function.
Care must be taken to avoid extravasation during intravenous administration as this may cause tissue damage and severe pain.

Care should be taken to avoid contact with the skin and eyes when reconstituting or administering dacarbazine.

4.5 Interaction with other medicinal products and other forms of interaction

Microsomal liver enzyme inducer eg. barbiturates, rifampicin, phenytoin may theoretically hasten the activation of dacarbazine to aminoimidazole-carboxamide.

Mercaptopurine, azathioprine, allopurinol: dacarbazine inhibits xanthine oxidase and may theoretically potentiate the activity of these drugs.

Patients receiving Dacarbazine should not receive immunisation with live vaccines. Dacarbazine may impair the immunological response to the vaccine with the development of a generalised vaccinia.

4.6 Pregnancy and lactation

Studies have demonstrated that this agent is carcinogenic and teratogenic when administered to animals. Dacarbazine therefore should not be administered to pregnant or lactating women unless the benefit clearly justifies the potential risk to the foetus.

4.7 Effects on ability to drive and use machines

Dacarbazine in appropriate doses should not impair the ability to drive. However, rare adverse reactions affecting the nervous system may cause blurred vision, seizures, headache, confusion, malaise and lethargy. Patients affected by these adverse effects should not drive or operate machinery.

4.8 Undesirable effects

Adverse Effects

Common Reactions

Symptoms of anorexia, nausea, and vomiting are the most frequent side-effects. Vomiting may last for 1-12 hours and is incompletely and unpredictably palliated with prochlorperazine. Diarrhoea is a rarer side-effect of Dacarbazine therapy. Rarely have intractable nausea and vomiting have necessitated discontinuation of therapy.

It is suggested that restriction of the patients oral fluid intake and food 4-6 hours prior to treatment may be helpful. The rapid toleration of these symptoms suggests a central nervous system mechanism, and usually these symptoms subside after the first 1-2 days.

Haematological: Bone marrow depression, leucocytopenia, thrombocytopenia.

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

Less Common Reactions

Cardiovascular: Facial flushing.

Dermatological: Transient rash, alopecia

General: Infrequently some patients have experienced an influenza type syndrome of fever, myalgias and malaise. This syndrome usually occurs after large single doses and approximately seven days after treatment with dacarbazine and lasts 7-21 days, and may reoccur with successive treatments.

Hepatic: Increases in transamineases (AST, ALT) alkaline phosphatase, LDH. Levels usually return to normal within two weeks; hepatic toxicity accompanied by hepatic vein thrombosis and hepatocellular necrosis, (Budd-Chiari Syndrome) resulting in death.

Nervous System: Blurred vision, seizures, headache, facial paraesthesia, confusion, malaise, lethargy.

Anaphylaxis can occur very rarely following administration of Dacarbazine.

Photosensitivity reactions may occur rarely.

4.9 Overdose

Signs and Symptoms:

Severe bone marrow depression and gastrointestinal effects such as nausea, vomiting and diarrhoea may be expected.

Treatment

Cease dacarbazine administration and institute supportive measures, eg. appropriate transfusion for bone marrow suppression.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dacarbazine is an imidazole dimethyltriazene with reproducible activity in patients with metastatic melanoma. The structure of Dacarbazine bears a striking resemblance to the metabolite 5-aminoimidazole-4-carboxamide (AIC) which is converted to inosinic acid by enzymes involved in purine synthesis.

It was therefore initially thought to act as an antimetabolite, by inhibiting purine metabolism and nucleic acid synthesis. However the similarity of structure is of little relevance since Dacarbazine is extensively metabolised by the cytochrome P450 system in the liver by N-demethylation reaction.

The monoemthyl derivative then spontaneously cleaves to yield AIC and an intermediate compound, probably diazomethane, which decomposes to produce the methyl carbonium ion. This ion attached to nucleophilic groups on nucleic acids and other macromolecules, thus acting as an alkylating agent. The 7-position of guanine on DNA is especially susceptible to alkylation.

Dacarbazine is thought to act as an alkylating agent in man. It interferes with the synthesis of DNA, RNA and proteins but its cytotoxicity is not specific for any phase of the cell cycle. In general, it is most effective in inhibiting synthesis of RNA. Dacarbazine kills cells slowly and no immunosuppressive action has been shown in man. There are no systemic studies of dose-response effects but one anecdotal report has suggested that there may be an increased chance of response as the dose increases.

Dacarbazine undergoes spontaneous photodegradation in light, decomposing into 5-diazoimidazole-4-carboxamide and dimethylamine. 5-Diazoimidazole-4-carboxamide can attack nucleophilic groups of DNA and also undergoes structural rearrangement to form 2-azahypoxanthine. However, the products of photodegradation of dacarbazine probably do not contribute greatly to its cytotoxicity, although they may be implicated in the local burning pain on intravenous injection and systemic problems associated with the drug.

5.2 Pharmacokinetic properties

The volume of distribution of dacarbazine exceeds body water content, suggesting localisation in some body tissues, probably the liver. Dacarbazine is only slightly (approximately 5%) bound to plasma proteins. Its plasma half-life after intravenous administration is approximately 35 minutes. In animal studies, approximately 46% of radio-labelled dose was recovered from the urine after 6 hours. Of this 46%, almost half, was unchanged dacarbazine and a similar quantity was amino-imidazole carboxamide, a metabolite. Dacarbazine is subject to renal tubular secretion rather than glomerular filtration.

Dacarbazine crosses the blood-brain barrier to a limited extent; CSF concentrations are reported to be about 14% of plasma concentrations. It is not known if dacarbazine crosses the placenta or distributes into milk.

5.3 Preclinical safety data

Not Applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid Monohydrate
Mannitol
Sodium Hydroxide 1.0 N (for pH adjustment only)

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products except for those mentioned in *section 6.6.*

Dacarbazine is incompatible with hydrocortisone sodium succinate in solution, forming an immediate precipitate.

It has been reported to be incompatible with heparin, although only with concentrated solutions (25 mg/ml).

6.3 Shelf Life

Prior to use:
3 years

In-use:
For single use only.
Discard any unused contents.

Contains no antimicrobial preservative.
If aseptic preparation cannot be ensured, the injection/infusion should be prepared immediately before use.

If the reconstituted/diluted solution, as directed in *section 6.6.*, has been aseptically prepared and 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 at 2 to 8°C and protected from light.

6.4 Special precautions for storage

Prior to use:
Store in a refrigerator (2°C – 8°C).
Keep the vial in the outer carton in order to protect from light

In-use:
Please refer to sections 6.3 and 6.6 for in-use storage precautions.

6.5 Nature and contents of container

20ml amber Type I glass vial, 20mm West Type 1816 rubber closure, aluminum cap with plastic 'flip-off' top (with or without Onco-Tain shink wrapping).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Handling precautions
Dacarbazine is cytotoxic and as with other potentially toxic compounds, caution should be exercised when handling and preparing dacarbazine preparations.

Refer to local cytotoxic handling guidelines before preparing injections or infusions.

Pregnant personnel should not handle cytotoxics.

The handling of this cytotoxic agent by healthcare personnel requires every precaution to guarantee the protection of the handler and his surroundings.

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the integrity of the medicinal product, the protection of the environment and in particular the protection of the personnel handling the medicines, in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area. Operations such as reconstitution of powder and transfer to syringes/infusion bags should be carried out only in the designated area.

The personnel carrying out these procedures must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.

Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers. See paragraph below on disposal.

If substance should come into contact with mucous membranes, wash immediately and thoroughly with water.

In case of contact of the drug with the eye, wash the eye thoroughly with water. If the substance is splashed accidentally onto the skin, wash the skin with large amounts of water and then with a soft soap. Rinse thoroughly.

Excreta and vomit must be handled with care.

Preparation instructions
Dacarbazine 100 mg and 200 mg vials should be reconstituted with 9.9 ml
and 19.7 ml respectively, with Water for Injections BP. Aseptically transfer the required amount of Water for Injections into the vial and shake until a solution is obtained. The resulting solutions contain the equivalent of 10 mg/ml of dacarbazine and have a pH of 3 to 4. The resultant solution should be injected intravenously over one to two minutes.

If desired the reconstituted solution can be further diluted with 125-250 ml of Dextrose Injection BP 5% or Sodium Chloride Injection BP 0.9% and administered by intravenous infusion over 15-30 minutes.

Prior to administration the solution should be clear, colourless to pale yellow and free from visible particles. Dacarbazine is photosensitive; exposure to light causing a colour change from pale yellow to pink. The product should not be used if it appears pink in colour.

During administration of an infusion, the infusion set should be protected from light, e.g. by using light-resistant PVC infusion sets. If normal infusion sets are used, then these should be covered to protect from light.

Disposal
Remnants of the medicinal product as well as all materials that have been used for reconstitution, dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents in accordance with local requirements related to the disposal of hazardous waste.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0437/040/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 May 1998

Date of last renewal: 15 May 2008

10 DATE OF REVISION OF THE TEXT

June 2009