The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

19 September 2002
CPMP/2020/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

SUMMARY INFORMATION ON A REFERRAL OPINION FOLLOWING AN ARBITRATION
PURSUANT TO ARTICLE 29 OF DIRECTIVE 2001/83/EC
(formerly Article 10, paragraph 2 of Directive 75/319/EEC of 20 May 1975 as amended)

for

Dacarbazine Faulding, 100 mg, 200 mg and 600 mg
Powder for solution for injection

International NonProprietary Name (INN): dacarbazine

BACKGROUND INFORMATION

Dacarbazine Faulding contains the active substance dacarbazine which is a cytotoxic agent, and is authorised in several EU Member States. It is indicated for the treatment of patients with metastatic malignant melanoma. Additional indications for dacarbazine as part of combination chemotherapy are:

- Hodgkin's disease
- Advanced adult soft tissue sarcomas (except mesothelioma, Kaposi sarcoma)

Member States which have previously authorised the above mentioned medicinal product under a national procedure are the United Kingdom, Portugal and Ireland (100 mg, 200 mg only). The applicant, Faulding Pharmaceuticals plc, sought to initiate a Mutual Recognition (MR) procedure with the UK as Reference Member State (RMS). Applications were submitted to 3 Concerned Member States, France, Spain and Ireland, between 12 – 13 July 2001, and the Mutual Recognition Procedure started on 1 August 2001.

No breakout session of the MRFG was held. However, several discussions on the SPC and quality aspects took place in October 2001, and as a consequence the applicant circulated revised SPCs to all concerned MS on 30 October 2001 (day 90 of the MRP). At this time quality objections from France remained unresolved.

On 6 November 2001, in view of the unresolved quality objections, France therefore issued a Notification of an official referral for Arbitration, (under Article 29 of Directive 2001/83, formerly Article 10, paragraph 2 of Directive 75/319/EEC of 20 May 1975 as amended) to the CPMP

The referral procedure started on 16 November 2001, when a List of Questions was sent to the applicant by the CPMP. The grounds for this arbitration procedure were based entirely on pharmaceutical quality issues:

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- the uncertain quality of the active substance and
- the uncertain quality of the finished product.

The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, Scientific discussion within the Committee and comments from the Marketing Authorisation Holder, was of the opinion that the objections raised by France had been resolved by the written representations made by the applicant during the arbitration procedure and should not prevent the granting of a Marketing Authorisation.

The CPMP therefore adopted a positive opinion, on 25 April 2002, recommending the maintenance of this product on the market, subject to a number of conditions relating to minor quality issues. The CPMP considered that the benefit/risk ratio of dacarbazine remained unchanged by this procedure and continues to be favourable for the agreed indications. The CPMP also adopted the latest MRP day 90 SPCs as an Annex to the opinion.

The list of product names concerned is given in the Annex I. The scientific conclusions are provided in the Annex II, together with the Summaries of Product Characteristics in Annex III and the conditions of the marketing authorisations in Annex IV.

The final opinion was converted into a Decision by the European Commission on 21 August 2002.

ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS, OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, APPLICANT / MARKETING AUTHORISATION HOLDER, PACKAGING AND PACKAGE SIZE IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Content	Package-size
UK	Faulding Pharmaceuticals Plc Queensway Royal Leamington Spa Warwickshire CV31 3RW, UK	Dacarbazine Faulding	100 mg	Powder for solution for injection	Intravenous use	Vial (glass)	10 ml	1 vial
UK	Faulding Pharmaceuticals Plc Queensway Royal Leamington Spa Warwickshire CV31 3RW, UK	Dacarbazine Faulding	200 mg	Powder for solution for injection	Intravenous use	Vial (glass)	20 ml	1 vial
UK	Faulding Pharmaceuticals Plc Queensway Royal Leamington Spa Warwickshire CV31 3RW, UK	Dacarbazine Faulding	600 mg	Powder for solution for injection	Intravenous use	Vial (glass)	100 ml	1 vial
France	Faulding Pharmaceuticals SA 93 Rue de Magenta 92600 Asnieres France	Dacarbazine Faulding	100 mg	Powder for solution for injection	Intravenous use	Vial (glass)	10 ml	1 vial
France	Faulding Pharmaceuticals SA 93 Rue de Magenta 92600 Asnieres France	Dacarbazine Faulding	200 mg	Powder for solution for injection	Intravenous use	Vial (glass)	20 ml	1 vial
France	Faulding Pharmaceuticals SA 93 Rue de Magenta 92600 Asnieres France	Dacarbazine Faulding	600 mg	Powder for solution for injection	Intravenous use	Vial (glass)	100 ml	1 vial

Member State	Marketing Authorisation Holder	Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Content	Package-size
Spain	Faulding Pharmaceuticals Plc Queensway Royal Leamington Spa Warwickshire CV31 3RW, UK	Dacarbazine Faulding	100 mg	Powder for solution for injection	Intravenous use	Vial (glass)	10 ml	1 vial
Spain	Faulding Pharmaceuticals Plc Queensway Royal Leamington Spa Warwickshire CV31 3RW, UK	Dacarbazine Faulding	200 mg	Powder for solution for injection	Intravenous use	Vial (glass)	20 ml	1 vial
Spain	Faulding Pharmaceuticals Plc Queensway Royal Leamington Spa Warwickshire CV31 3RW, UK	Dacarbazine Faulding	600 mg	Powder for solution for injection	Intravenous use	Vial (glass)	100 ml	1 vial

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF DACARBAZINE POWDER FOR SOLUTION FOR INJECTION

1. Quality issues

Uncertain quality of the active substance

Concerning the evaluation of the quality of the active substance, it seems there had been a misunderstanding regarding the European DMF procedure concerning the names of manufacturers and DMF holders and the relationship between the firms Sapec, Rohner and Amcis.
The CPMP now considers that Sapec, the EDMF Holder, has two manufacturers for its dacarbazine, bulk material: Rohner (originally) and Amcis (new). The latter manufacturer was introduced though a variation type I and accepted by the RMS. However, the French EDMF did not appear to have been updated to include Sapec, i.e. Sapec appear not to have routinely submitted supplements to the Applicants Part of DMF to the French authorities.

There was also a question relating to the introduction of a new HPLC method for analysing impurities in the active substance by the DMF owner (Sapec) in their DMF supplement dated 18th July 2001.
As Faulding agrees to test the active substance according to the British Pharmacopoeia (BP) method and to introduce later the new method via a variation, this issue is regarded as being solved.

Uncertain quality of the finished product

Concerning doubts about the quality of the finished product, these centred on the analytical methods used for impurities. The proposed analytical procedure for 2-azahypoxanthone and related substances test is very similar to the BP method, and it has been validated and cross-validated with regard to the BP method. Faulding has demonstrated during validation that the peaks in the chromatogram eluted before 2-azahypoxanthone arises from excipients and/or the dissolution medium. The same reasoning applies for 5-aminoimidazole-4-carboxamide.
Therefore this issue is now solved.

There was an objection that no finished product appears to have been manufactured with all the suppliers of active substance as cited in the dossier. Faulding believes that approval of these Marketing Authorisation Applications with Amcis AG as an alternative manufacturing site of the raw material, would not constitute grounds for concern that the product may present a risk to public health, despite the fact that no finished product has yet been manufactured using Amcis material.
As had already been clarified during the question and answer phase of the MRP, the Amcis site of manufacture of the Dacarbazine active substance was added to the Marketing Authorisation in the Reference Member State by way of a Type I variation which was approved in March 2000 following the receipt of a supplement to the Sapec DMF. CPMP considered that the answer of Faulding was acceptable. Dacarbazine bulk material from the two manufacturers have identical specification and the physico-chemical properties are not critical for this type of dosage form (injection). The submission of results of batch analysis of the injections, produced with AMCIS material, prior to the authorisation was not considered necessary.

2. Efficacy and Safety issues:

There were no direct efficacy or safety issues in dispute during this arbitration procedure. It was implied that the quality issues may have consequences, particularly with regard to initial doubts over the control of impurities which may have safety consequences. However, these were resolved as summarised above.

CONCLUSIONS

The Benefit/Risk ratio for this product is still favourable and remained unchanged at the end of this arbitration procedure.

The CPMP having considered -

- The MRP assessment report of the RMS,
- the issues for arbitration,
- the written responses provided by the company,
- the Rapporteur/Co-Rapporteur's assessment report on these responses,
- comments from CPMP members,

concluded that the pharmaceutical quality objections raised by France have been resolved by the written representations made by the applicant during this arbitration procedure and should not prevent the granting of a Marketing Authorisation. The CPMP also adopted SPCs (Annex III).

At the time of the CPMP opinion a number of minor quality concerns remained, having no impact on the benefit/risk balance of the product. Therefore, the CPMP recommended that these should be dealt with as conditions, defined in Annex IV.

Following the CPMP Opinion on the scientific issues for arbitration, a Decision was issued by the European Commission on 21 August 2002.

ANNEX III

SUMMARIES OF PRODUCT CHARACTERISTICS

Note: These SPCs are those that were Annexed to the Commission Decision on this referral for arbitration, and the texts were valid at that time.

They are not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current texts.

1. NAME OF THE MEDICINAL PRODUCT

Dacarbazine Faulding 100 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial contains 100 mg of dacarbazine.

When reconstituted each ml of solution contains 10 mg of dacarbazine.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A white or pale yellow powder or plug.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Further indications for dacarbazine as part of combination chemotherapy are:
- Hodgkin's disease
- Advanced adult soft tissue sarcomas (except mesothelioma, Kaposi sarcoma)

4.2 Posology and method of administration

Dosage

The following regimes can be used.

Malignant Melanoma

Dacarbazine can be administered 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.

Hodgkin's Disease

Dacarbazine is administered in a daily dose of 375 mg/m^2 body surface area i.v. on day 1 and day 15 in combination with doxorubicin, bleomycin and vinblastine for each cycle of ABVD regimen.

Adult 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 count should be conducted as well as monitoring of hepatic and renal function. Since severe gastrointestinal reactions frequently occur, antiemetic and supportive measures are advisable. 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.

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 adverse effects of dacarbazine. In Hodgkin's disease, the recommended cycles for administration of ABVD combination therapy ranges between 3 to 8 cycles of therapy based on the stage of disease and the treatment response. In metastasised malignant melanoma and in advanced tissue sarcoma, the duration of treatment depends on the efficacy and tolerability in the individual patient.

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 use in elderly patients can be given.

Administration

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

If extravasation occurs, the injection should be discontinued immediately.

Dacarbazine is sensitive to light exposure. All reconstituted solutions should be suitably protected from light during administration (light-resistant infusion set).

Administration is by the intravenous route only.

Dacarbazine 100 mg and 200 mg 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 10 mg/ml of dacarbazine and have a pH of 3 to 4. The resultant solution is hypo-osmolar and therefore should be given by slow intravenous injection 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.

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

Instructions for handling

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 protection of the environment and, in particular, the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Personnel 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 and collection bags for waste.

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

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.

4.3 Contraindications

This medicinal product is contraindicated in cases of:

- Patients who have demonstrated a hypersensitivity to dacarbazine in the past
- Patients with severe liver or kidney diseases
- Pregnancy and lactation
- In combination with yellow fever vaccine, phenytoin in prophylactic use, and live attenuated vaccines (see 4.5, Interactions with other medicaments and other forms of interaction)

4.4 Special warnings and special 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. Therefore frequent monitoring of liver size, function and blood counts (especially eosinophils) is required (see 4.8).

It is recommended that dacarbazine be administered by physicians experienced in the use of cytotoxic therapy. Laboratory facilities should be available for blood monitoring.

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.

Precautions for Use

Hepatotoxic drugs and alcohol should be avoided during chemotherapy.

Administration of an anti-emetic may also reduce the severity of gastrointestinal effects.

Impairment of renal and liver function: See dosage in impaired renal and liver function.

If extravasation occurs, tissue damage and severe pain may occur.

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

Interactions common to all cytotoxics

Due to the increase of thrombotic risk in case of tumeral 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 contraindicated

- Phenytoin (in prophylactic use – convulsivant effect). Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug.
- Yellow fever vaccine: risk of fatal systemic vaccinal disease.

Concomitant use not recommended

- Live attenuated vaccines: risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Use an inactivated vaccine where this exists (poliomyelitis).

Concomitant use requiring precautions of use

- Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug. Administer momentarily an anticonvulsant benzodiazepine.

Concomitant use to take into consideration

Cyclosporin (and by extrapolation Tacrolimus): Excessive immunosuppression with risk of lymphoproliferation.

Specific interactions of Dacarbazine (high dose) requiring precautions of use

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.

4.6 Pregnancy and lactation

Contraceptive measures

Men are advised to take contraceptive measures during and for 3 months after cessation of therapy.
Women of childbearing age should use effective methods of contraception during the treatment.

Pregnancy

For Dacarbazine no clinical data on exposed pregnancy are available. Studies in animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown.
Dacarbazine is contraindicated during pregnancy (see 4.3).

Lactation

Dacarbazine is contraindicated during lactation (see 4.3).

4.7 Effects on ability to drive and use machines

Dacarbazine may influence the ability to drive or operate machinery in case of nausea and vomiting or rare adverse reactions affecting the nervous system.

4.8 Undesirable effects

Common Reactions

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

Haematological: bone marrow depression, leucocytopenia, thrombocytopenia and occasionally anaemia (see 4.4).

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. Venous irritation and some of the systemic adverse reactions are thought to result from formation of photodegredation products.

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

Renal: Impaired renal function with increased blood levels of creatinine and urea.

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

Anaphylaxis (erythema, maculopapular exanthema or urticaria) can occur very rarely following administration of dacarbazine.

Photosensitivity reactions may rarely occur.

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 overdosage is only suspected, long-term careful haematological monitoring is essential and supportive measures, e.g. appropriate transfusions for bone marrow suppression may be required. There is no known antidote for dacarbazine overdose. Therefore, special care has to be taken to avoid overdose of this drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC: L01AX04

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 monomethyl 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

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 and sodium hydroxide.

6.2 Incompatibilities

Dacarbazine is incompatible with hydrocortisone sodium succinate in solution, forming an immediate precipitate. It is also incompatible with L-cysteine and sodium hydrogen carbonate.

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

Dacarbazine must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at 2-8°C. Keep vial in the outer carton.

The reconstituted and diluted solutions should be protected from light.

The physical and chemical in-use stability:

	Storage conditions
Reconstituted solution	96 hours at 2-8°C
Further diluted with 5% dextrose or 0.9% sodium chloride	24 hours at 2-8°C

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 not be longer than 24 hours at 2 to 8°C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

20mm West Type 1 1816 S87J freeze-drying rubber closure.

10ml amber Type I glass vials with or without Onco-Tain™ shrink wrapping.

Aluminium cap with plastic 'flip-off' top.

6.6 Instructions for use and handling and disposal

Cytotoxic Handling Guidelines

The handling of this cytotoxic agent by nursing or medical personnel requires every precaution to guarantee the protection of the handler and their surroundings (see 4.2 Posology and Method of Administration).

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.

Before being administered, injectable solution should be visually inspected in order to detect possible presence of particles of discolouration.

Preparation Guidelines

All operations such as reconstitution should be carried out only under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.

Dacarbazine solutions should be prepared immediately before use. Before being administered, injectable solution should be visually inspected in order to detect possible presence of particles of discolouration. Dacarbazine is photosensitive, with exposure to light causing a colour change from pale yellow to pink. The product should not be used if it appears pink in colour.

Aseptically transfer the required amount of water for injections into the vial and shake until a solution is obtained. The solution should be clear, colourless and free from visible particles. 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 5% or Sodium Chloride Injection 0.9% and administered by intravenous infusion over 15-30 minutes. During administration, the infusion set should be protected from exposure to daylight 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

Vials, materials that have been utilised for dilution, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated.

7. MARKETING AUTHORISATION HOLDER

Faulding Pharmaceuticals plc

Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04515/0091

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Dacarbazine Faulding 200 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial contains 200 mg of dacarbazine.

When reconstituted each ml of solution contains 10 mg of dacarbazine.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A white or pale yellow powder or plug.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Further indications for dacarbazine as part of combination chemotherapy are:
- Hodgkin's disease
- Advanced adult soft tissue sarcomas (except mesothelioma, Kaposi sarcoma)

4.2 Posology and method of administration

Dosage

The following regimes can be used.

Malignant Melanoma

Dacarbazine can be administered 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.

Hodgkin's Disease

Dacarbazine is administered in a daily dose of 375 mg/m^2 body surface area i.v. on day 1 and day 15 in combination with doxorubicin, bleomycin and vinblastine for each cycle of ABVD regimen.

Adult 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 count should be conducted as well as monitoring of hepatic and renal function. Since severe gastrointestinal reactions frequently occur, antiemetic and supportive measures are advisable. 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.

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 adverse effects of dacarbazine. In Hodgkin's disease, the recommended cycles for administration of ABVD combination therapy ranges between 3 to 8 cycles of therapy based on the stage of disease and the treatment response. In metastasised malignant melanoma and in advanced tissue sarcoma, the duration of treatment depends on the efficacy and tolerability in the individual patient.

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 use in elderly patients can be given.

Administration

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

If extravasation occurs, the injection should be discontinued immediately.

Dacarbazine is sensitive to light exposure. All reconstituted solutions should be suitably protected from light during administration (light-resistant infusion set).

Administration is by the intravenous route only.

Dacarbazine 100 mg and 200 mg 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 10 mg/ml of dacarbazine and have a pH of 3 to 4. The resultant solution is hypo-osmolar and therefore should be given by slow intravenous injection 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.

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

Instructions for handling

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 protection of the environment and, in particular, the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Personnel 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 and collection bags for waste.

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

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.

4.3 Contraindications

This medicinal product is contraindicated in cases of:

- Patients who have demonstrated a hypersensitivity to dacarbazine in the past
- Patients with severe liver or kidney diseases
- Pregnancy and lactation
- In combination with yellow fever vaccine, phenytoin in prophylactic use, and live attenuated vaccines (see 4.5, Interactions with other medicaments and other forms of interaction)

4.4 Special warnings and special 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. Therefore frequent monitoring of liver size, function and blood counts (especially eosinophils) is required (see 4.8).

It is recommended that dacarbazine be administered by physicians experienced in the use of cytotoxic therapy. Laboratory facilities should be available for blood monitoring.

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, particulary with regards to the haemopoietic toxicity.

Precautions for Use

Hepatotoxic drugs and alcohol should be avoided during chemotherapy.

Administration of an anti-emetic may also reduce the severity of gastrointestinal effects.

Impairment of renal and liver function: See dosage in impaired renal and liver function.

If extravasation occurs, tissue damage and severe pain may occur.

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

Interactions common to all cytotoxics

Due to the increase of thrombotic risk in case of tumeral 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 contraindicated

- Phenytoin (in prophylactic use – convulsivant effect). Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug.
- Yellow fever vaccine: risk of fatal systemic vaccinal disease.

Concomitant use not recommended

- Live attenuated vaccines: risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Use an inactivated vaccine where this exists (poliomyelitis).

Concomitant use requiring precautions of use

- Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug. Administer momentarily an anticonvulsant benzodiazepine.

Concomitant use to take into consideration

Cyclosporin (and by extrapolation Tacrolimus): Excessive immunosuppression with risk of lymphoproliferation.

Specific interactions of Dacarbazine (high dose) requiring precautions of use

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.

4.6 Pregnancy and lactation

Contraceptive measures

Men are advised to take contraceptive measures during and for 3 months after cessation of therapy.
Women of childbearing age should use effective methods of contraception during the treatment.

Pregnancy

For Dacarbazine no clinical data on exposed pregnancy are available. Studies in animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown.
Dacarbazine is contraindicated during pregnancy (see 4.3).

Lactation

Dacarbazine is contraindicated during lactation (see 4.3).

4.7 Effects on ability to drive and use machines

Dacarbazine may influence the ability to drive or operate machinery in case of nausea and vomiting or rare adverse reactions affecting the nervous system.

4.8 Undesirable effects

Common Reactions

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

Haematological: bone marrow depression, leucocytopenia, thrombocytopenia and occasionally anaemia (see 4.4).

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. Venous irritation and some of the systemic adverse reactions are thought to result from formation of photodegredation products.
Hepatic:	Increases in transaminases (AST, ALT), alkaline phosphatase, LDH. Levels usually return to normal within two weeks; hepatic toxicity accompanied by hepatic vein thrombosis and hepatic necrosis (Budd-Chiari Syndrome) resulting in death.
Renal:	Impaired renal function with increased blood levels of creatinine and urea.
Nervous System:	Blurred vision, seizures, headache, facial paraesthesia, confusion, malaise, and lethargy.

Anaphylaxis (erythema, maculopapular exanthema or urticaria) can occur very rarely following administration of dacarbazine.

Photosensitivity reactions may rarely occur.

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 overdosage is only suspected, long-term careful haematological monitoring is essential and supportive measures, e.g. appropriate transfusions for bone marrow suppression may be required. There is no known antidote for dacarbazine overdose. Therefore, special care has to be taken to avoid overdose of this drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC: L01AX04

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 monomethyl 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

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 and sodium hydroxide.

6.2 Incompatibilities

Dacarbazine is incompatible with hydrocortisone sodium succinate in solution, forming an immediate precipitate. It is also incompatible with L-cysteine and sodium hydrogen carbonate.

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

Dacarbazine must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at 2-8°C. Keep vial in the outer carton.

The reconstituted and diluted solutions should be protected from light.

The physical and chemical in-use stability:

	Storage conditions
Reconstituted solution	96 hours at 2-8°C
Further diluted with 5% dextrose or 0.9% sodium chloride	24 hours at 2-8°C

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 not be longer than 24 hours at 2 to 8°C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

20mm West Type 1 1816 S87J freeze-drying rubber closure.

20ml amber Type I glass vials with or without Onco-Tain™ shrink wrapping.

Aluminium cap with plastic 'flip-off' top.

6.6 Instructions for use and handling and disposal

Cytotoxic Handling Guidelines

The handling of this cytotoxic agent by nursing or medical personnel requires every precaution to guarantee the protection of the handler and their surroundings (see 4.2 Posology and Method of Administration).

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.

Before being administered, injectable solution should be visually inspected in order to detect possible presence of particles of discolouration.

Preparation Guidelines

All operations such as reconstitution should be carried out only under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.

Dacarbazine solutions should be prepared immediately before use. Before being administered, injectable solution should be visually inspected in order to detect possible presence of particles of discolouration. Dacarbazine is photosensitive, with exposure to light causing a colour change from pale yellow to pink. The product should not be used if it appears pink in colour.

Aseptically transfer the required amount of water for injections into the vial and shake until a solution is obtained. The solution should be clear, colourless and free from visible particles. 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 5% or Sodium Chloride Injection 0.9% and administered by intravenous infusion over 15-30 minutes. During administration, the infusion set should be protected from exposure to daylight 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

Vials, materials that have been utilised for dilution, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated.

7. MARKETING AUTHORISATION HOLDER

Faulding Pharmaceuticals plc
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04515/0092

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Dacarbazine Faulding 600 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial contains 600 mg of dacarbazine.

When reconstituted each ml of solution contains 10 mg of dacarbazine.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A white or pale yellow powder or plug.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Further indications for dacarbazine as part of combination chemotherapy are:
- Hodgkin's disease
- Advanced adult soft tissue sarcomas (except mesothelioma, Kaposi sarcoma)

4.2 Posology and method of administration

Dosage

The following regimes can be used.

Malignant Melanoma

Dacarbazine can be administered 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.

Hodgkin's Disease

Dacarbazine is administered in a daily dose of 375 mg/m^2 body surface area i.v. on day 1 and day 15 in combination with doxorubicin, bleomycin and vinblastine for each cycle of ABVD regimen.

Adult 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 count should be conducted as well as monitoring of hepatic and renal function. Since severe gastrointestinal reactions frequently occur, antiemetic and supportive measures are advisable. 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.

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 adverse effects of dacarbazine. In Hodgkin's disease, the recommended cycles for administration of ABVD combination therapy ranges between 3 to 8 cycles of therapy based

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

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 use in elderly patients can be given.

Administration

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

If extravasation occurs, the injection should be discontinued immediately.

Dacarbazine is sensitive to light exposure. All reconstituted solutions should be suitably protected from light during administration (light-resistant infusion set).

Administration is by the intravenous route only.

Dacarbazine 100 mg and 200 mg 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 10 mg/ml of dacarbazine and have a pH of 3 to 4. The resultant solution is hypo-osmolar and therefore should be given by slow intravenous injection 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.

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

Instructions for handling

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 protection of the environment and, in particular, the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Personnel 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 and collection bags for waste.

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

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.

4.3 Contraindications

This medicinal product is contraindicated in cases of:

- Patients who have demonstrated a hypersensitivity to dacarbazine in the past
- Patients with severe liver or kidney diseases
- Pregnancy and lactation
- In combination with yellow fever vaccine, phenytoin in prophylactic use, and live attenuated vaccines (see 4.5, Interactions with other medicaments and other forms of interaction)

4.4 Special warnings and special 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. Therefore frequent monitoring of liver size, function and blood counts (especially eosinophils) is required (see 4.8).

It is recommended that dacarbazine be administered by physicians experienced in the use of cytotoxic therapy. Laboratory facilities should be available for blood monitoring.

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.

Precautions for Use

Hepatotoxic drugs and alcohol should be avoided during chemotherapy.

Administration of an anti-emetic may also reduce the severity of gastrointestinal effects.

Impairment of renal and liver function: See dosage in impaired renal and liver function.

If extravasation occurs, tissue damage and severe pain may occur.

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

Interactions common to all cytotoxics

Due to the increase of thrombotic risk in case of tumeral 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 contraindicated

- Phenytoin (in prophylactic use – convulsivant effect). Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug.
- Yellow fever vaccine: risk of fatal systemic vaccinal disease.

Concomitant use not recommended

- Live attenuated vaccines: risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Use an inactivated vaccine where this exists (poliomyelitis).

Concomitant use requiring precautions of use

- Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug. Administer momentarily an anticonvulsant benzodiazepine.

Concomitant use to take into consideration

Cyclosporin (and by extrapolation Tacrolimus): Excessive immunosuppression with risk of lymphoproliferation.

Specific interactions of Dacarbazine (high dose) requiring precautions of use

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.

4.6 Pregnancy and lactation

Contraceptive measures

Men are advised to take contraceptive measures during and for 3 months after cessation of therapy.
Women of childbearing age should use effective methods of contraception during the treatment.

Pregnancy

For Dacarbazine no clinical data on exposed pregnancy are available. Studies in animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown.
Dacarbazine is contraindicated during pregnancy (see 4.3).

Lactation

Dacarbazine is contraindicated during lactation (see 4.3).

4.7 Effects on ability to drive and use machines

Dacarbazine may influence the ability to drive or operate machinery in case of nausea and vomiting or rare adverse reactions affecting the nervous system.

4.8 Undesirable effects

Common Reactions

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

Haematological: bone marrow depression, leucocytopenia, thrombocytopenia and occasionally anaemia (see 4.4).

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. Venous irritation and some of the systemic adverse reactions are thought to result from formation of photodegredation products.
Hepatic:	Increases in transaminases (AST, ALT), alkaline phosphatase, LDH. Levels usually return to normal within two weeks; hepatic toxicity accompanied by hepatic vein thrombosis and hepatic necrosis (Budd-Chiari Syndrome) resulting in death.
Renal:	Impaired renal function with increased blood levels of creatinine and urea.
Nervous System:	Blurred vision, seizures, headache, facial paraesthesia, confusion, malaise, and lethargy.

Anaphylaxis (erythema, maculopapular exanthema or urticaria) can occur very rarely following administration of dacarbazine.

Photosensitivity reactions may rarely occur.

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 overdosage is only suspected, long-term careful haematological monitoring is essential and

supportive measures, e.g. appropriate transfusions for bone marrow suppression may be required. There is no known antidote for dacarbazine overdose. Therefore, special care has to be taken to avoid overdose of this drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC: L01AX04

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 monomethyl 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

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 and sodium hydroxide.

6.2 Incompatibilities

Dacarbazine is incompatible with hydrocortisone sodium succinate in solution, forming an immediate precipitate. It is also incompatible with L-cysteine and sodium hydrogen carbonate.

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

Dacarbazine must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at 2-8°C. Keep vial in the outer carton.

The reconstituted and diluted solutions should be protected from light.

The physical and chemical in-use stability:

	Storage conditions
Reconstituted solution	96 hours at 2-8°C
Further diluted with 5% dextrose or 0.9% sodium chloride	24 hours at 2-8°C

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 not be longer than 24 hours at 2 to 8°C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

20mm West Type 1 1816 S87J freeze-drying rubber closure.

100ml amber Type I glass vials with or without Onco-Tain™ shrink wrapping.

Aluminium cap with plastic 'flip-off' top.

6.6 Instructions for use and handling and disposal

Cytotoxic Handling Guidelines

The handling of this cytotoxic agent by nursing or medical personnel requires every precaution to guarantee the protection of the handler and their surroundings (see 4.2 Posology and Method of Administration).

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.

Before being administered, injectable solution should be visually inspected in order to detect possible presence of particles of discolouration.

Preparation Guidelines

All operations such as reconstitution should be carried out only under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.

Dacarbazine solutions should be prepared immediately before use. Before being administered, injectable solution should be visually inspected in order to detect possible presence of particles of discolouration. Dacarbazine is photosensitive, with exposure to light causing a colour change from pale yellow to pink. The product should not be used if it appears pink in colour.

Aseptically transfer the required amount of water for injections into the vial and shake until a solution is obtained. The solution should be clear, colourless and free from visible particles. 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 5% or Sodium Chloride Injection 0.9% and administered by intravenous infusion over 15-30 minutes. During administration, the infusion set should be protected from exposure to daylight 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

Vials, materials that have been utilised for dilution, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated.

7. MARKETING AUTHORISATION HOLDER

Faulding Pharmaceuticals plc
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04515/0123

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

Conditions of the Marketing Authorisations

Dacarabazine 100 mg powder for solution for injection
Dacarabazine 200 mg powder for solution for injection
Dacarabazine 600 mg powder for solution for injection

Whilst there were no major issues of concern at the end of the arbitration process, the CPMP felt it was necessary to impose upon Faulding Pharmaceuticals plc some additional work in order to confirm the satisfactory quality of the active substance and finished product, and by implication, the satisfactory efficacy and safety of the product.

Therefore, having already confirmed that Amcis is the only manufacturer of the active substance, Faulding Pharmaceuticals plc provided a letter of commitment to carry out additional studies and provide results by the agreed deadlines as follows: -

- To provide stability data on the active substance manufactured by Amcis, by 30 November 2002.

- To provide 6-months stability data on the finished product made with active substance manufactured by Amcis, by 30 November 2002.

Faulding Pharmaceuticals plc also gave a commitment to submit any variations which may be necessary arising from the evaluation of this information.