PRODUCT MONOGRAPH

[Pr]Dacarbazine for Injection BP

600 mg/vial

Sterile Powder for Solution

Antineoplastic Agent

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

Date of Revision:
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Control Number: 221511

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Sterile Powder for Solution

THERAPEUTIC CLASSIFICATION
Antineoplastic Agent

CAUTION

Dacarbazine for Injection BP is a potent drug and should be used only by physicians experienced with cancer chemotherapeutic drugs (see **WARNINGS** and **PRECAUTIONS).** Blood counts should be taken at frequent intervals during and post therapy. MONITORING OF LIVER AND KIDNEY FUNCTIONS DURING THERAPY is advised (see **PRECAUTIONS).**

ACTIONS

Dacarbazine for Injection BP is a cell-cycle, non-specific antineoplastic agent. It is a structural analogue of 5-amino-imidazole-4-carboxamide which is an intermediate in purine biosynthesis. The exact mechanism of action of dacarbazine is not known. It may function as an alkylating agent, possibly after activation by metabolism in the liver, but other hypotheses, including inhibition of DNA synthesis by acting as a purine analogue and interaction with sulfhydryl groups, have also been proposed.

INDICATIONS AND CLINICAL USES

Palliative therapy of metastatic malignant melanoma.

CONTRAINDICATIONS

Dacarbazine for Injection BP is contraindicated in patients with known hypersensitivity to dacarbazine, and in patients who have previously had severe myelosuppression.

WARNINGS

It is recommended that Dacarbazine for Injection BP be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Dacarbazine for Injection BP should be administered to patients who are hospitalized and who can be observed carefully and frequently during and after therapy.

Dacarbazine for Injection BP is toxic to the hemopoietic system and may produce depression of the bone marrow, anemia, leukopenia, thrombocytopenia and bleeding (see **PRECAUTIONS**).

Nausea, vomiting, diarrhea, anorexia, and influenza-like syndrome may accompany the therapy.

Significant impairment of liver and kidney function can occur. Hepatic necrosis has been reported (see **PRECAUTIONS**).

If used in combination with other cytotoxic agents, the toxic effects may be potentiated.

Anaphylaxis can occur following the administration of Dacarbazine for Injection BP.

Carcinogenicity

Studies in mice and rats have demonstrated this agent to have a carcinogenic potential. An increased incidence of lung tumours, lymphomas, uterine tumours and splenic hemangiomas was found in mice administered 25 or 50 mg/kg dacarbazine intraperitoneally 3 times per week for 6 months. In rats, an increased incidence of tumours, including mammary tumours, lymphosarcomas and adenocarcinomas was noted after administration of 250 or 400 mg dacarbazine intraperitoneally as single injections. The significance of these results in relation to the dosages and dose schedules administered clinically is not known.

Use in Pregnancy

Safety in pregnancy has not been established. Dacarbazine has been shown to be mutagenic, carcinogenic and teratogenic in animal studies. When administered intraperitoneally to rats at doses of 50 mg/kg/day or

greater (approximately 11 times the human dose) teratogenic effects have been observed, including anomalies of the skeletal system, eyes, cardiovascular system and abdominal wall. Teratogenic effects have also been observed in rabbits administered 10 mg/kg intraperitoneally (approximately twice the human dose). There are no adequate and well-controlled studies in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of child-bearing potential should be advised to avoid becoming pregnant.

Contraceptive measures

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

Immunization/Vaccines

Dacarbazine is a moderate immunosuppressive agent. Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including dacarbazine, may result in serious or fatal infections. Vaccination with a live-attenuated vaccine should be avoided in patients receiving dacarbazine, or administrated no sooner than 3 months after the completion of chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

PRECAUTIONS

General

In the treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit against the risk of toxicity.

Hemopoietic depression may be severe and lead to fatality. A careful monitoring of hematologic changes is required during and after therapy. Significant hemopoietic toxicity may warrant temporary suspension or cessation of Dacarbazine for Injection BP therapy.

Leukocytopenia is usually seen 14 days after commencement of therapy, but has been noted as early as day 10 and, in 10% of patients, as late as day 30. The average duration is one week, and the longest is 3 weeks. Thrombocytopenia is most frequently seen 18 days after commencement of therapy, but in 43% of patients it has been noted by day 12 and in 10% not until after day 30. The average duration is one week, and the longest is 3 weeks.

Gastrointestinal symptoms: Anorexia, nausea and vomiting are experienced in over 90% of patients with the initial doses. Restriction of food and fluid intake for 4 to 6 hours prior to treatment is recommended. This symptomatology apparently is induced via a central nervous system mechanism. After the first few days of treatment the gastrointestinal symptoms tend to subside. Nausea and vomiting may last 1 to 12 hours and it may be completely but unpredictably palliated with phenobarbital and/or prochlorperazine. Rarely, intractable nausea and vomiting may necessitate discontinuance of the drug. Diarrhea is uncommon but has also been reported. When present, it is not severe.

There have been reports of significant impairment of liver and kidney function. Fatal hepatotoxicity due to hepatic vascular occlusion has been reported rarely, and has generally been observed during the second course of treatment with dacarbazine. In some cases this has been preceded by mild, transient hepatic toxicity after the first course of treatment. Monitoring of liver and kidney function is recommended.

Less than 10% of patients have experienced an influenza-like syndrome of fever to 39°C, myalgia and malaise. These symptoms most frequently occur after large single doses, some 2 to 7 days after treatment and last for 7 to 21 days. On successive treatments this syndrome may recur. In these cases, supportive management is recommended.

During intravenous administration of Dacarbazine for Injection BP, care should be exercised to avoid subcutaneous or perivascular extravasation. Extravasation may result in tissue damage, necrosis and severe pain.

Use in Children

Adequate studies on the use of dacarbazine in children have not been performed.

Use in the Elderly

Adequate studies on the use of dacarbazine in elderly patients have not been performed.

Nursing Mothers

It is not known whether dacarbazine is distributed into breast milk. Due to the potential risk to the infant, Dacarbazine for Injection BP should not be administered to nursing mothers.

Impaired hepatic and renal function

As dacarbazine is partially metabolised by the liver and is excreted primarily in the urine, impairment of hepatic and renal function is likely to necessitate a variation in dosage.

Drug Interactions

Dacarbazine has been used in combination with a variety of other antineoplastic agents. The potential for an increased incidence or severity of adverse reactions must be considered when combining dacarbazine with other agents.

A study in which fotemustine (100 mg/m^2) and dacarbazine (400 to 1000 mg/m^2) were administered sequentially resulted in a 14% incidence of fatal lung toxicity, in the form of adult respiratory distress syndrome.

It has been noted that administration of dacarbazine and interleukin-2 may result in alterations to the pharmacokinetics of dacarbazine. An increased clearance (of approximately 38%) and volume of distribution (of approximately 36%) have been reported when doses of 2 to 4 x 10^6 U/m^2 interleukin-2 were used. This alteration appears to correlate with the dose of interleukin-2 and should be taken into account, particularly when high doses of interleukin-2 are combined with dacarbazine.

It has been reported that dacarbazine reduced the response to levodopa in a patient with Parkinson's disease. The mechanism of this interaction is unclear, but since the plasma levels of levodopa were unchanged, it is unlikely to be due to pharmacokinetic changes.

Since the metabolism of dacarbazine involves microsomal liver enzymes, drugs which induce these enzymes, such as barbiturates, rifampicin and phenytoin, may theoretically enhance the metabolism of dacarbazine to aminoimidazole carboxamide (AIC).

Dacarbazine inhibits xanthine oxidase, and may theoretically potentiate the activity of drugs activated by this enzyme, such as mercaptopurine, azathioprine and allopurinol.

ADVERSE REACTIONS

The most common adverse reaction observed after administration of dacarbazine is depression of the hemopoietic system. Leukopenia and thrombocytopenia may be severe and lead to fatality. In addition, anorexia, nausea and vomiting occur in over 90% of patients after initial doses. Other adverse reactions reported less commonly are:

Cardiovascular: Facial flushing, EKG abnormalities, orthostatic hypotension. Hypotension appears to be associated with high doses (>850 mg/m^2).

CNS/Neuromuscular: Facial paresthesia, blurred vision, seizures, headache, confusion, malaise, lethargy, facial paresthesia.

Dermatological: Alopecia, erythematous or urticarial rash, reaction resembling fixed drug eruption. Rarely, photosensitivity, facial flushing.

Gastrointestinal: Diarrhea.

Hepatic: Hepatic dysfunction. Rarely, fatal hepatotoxicity, Budd-Chiari syndrome, hepatic vein thrombosis.

Hypersensitivity: Anaphylaxis has occurred occasionally. **Miscellaneous:** Influenza-like syndrome.

Renal: Kidney function impairment.

Local Tolerance

Local pain at the injection site may occur. Extravasation may result in tissue damage and severe pain.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Accidental overdosage with Dacarbazine for Injection BP would be expected to intensify hemopoietic depression and gastrointestinal symptomatology. Treatment should be supportive, with particular attention to fluid balance in the acute phase. The hemopoietic system should be closely monitored and appropriate therapy instituted on the basis of these findings.

For management of a suspected overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

The following schedule is recommended: 2 to 4.5 mg/kg/day for 10 days which may be repeated at 3-week intervals. An alternate recommended dosage is 200 to 250 mg/m^2 of body surface/day intravenously for 5 days. It has been found that dacarbazine may be as efficacious at the lower dosage as at the higher dosage.

Combinations of cancer chemotherapeutic agents have often shown an improved response over the use of single agents.

The 600 mg vial of Dacarbazine for Injection BP is reconstituted with 59.1 mL of Sterile Water for Injection, USP. The resulting solution contains an equivalent of 10 mg/mL of dacarbazine having a pH of 3.0 to 4.0. After the solution has been prepared, the calculated dose of the resulting solution is drawn into a syringe and injected **only** intravenously. Injection of Dacarbazine for Injection BP may be completed in approximately one minute. **Single use vials. Discard unused portion.** At room temperature the solution is not stable for more than 8 hours.

If desired, the reconstituted solution may be further diluted with 150 to 250 mL of 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP and administered as an intravenous infusion over a period of 15 to 30 minutes.

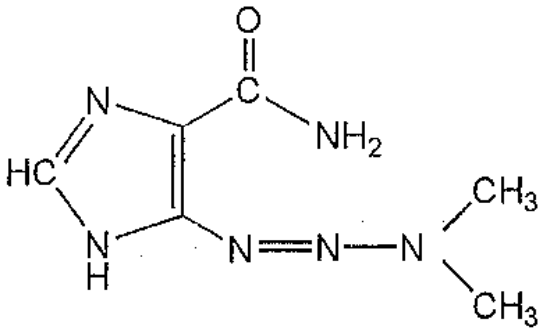
PHARMACEUTICAL INFORMATION

DrugSubstance

Proper Name: dacarbazine

Chemical Name: 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide

Chemical Structure:



Molecular Formula: $C_6H_{10}N_6O$

Molecular Weight: 182.188

Description: Colorless to pale yellow crystalline solid, sensitive to light. Slightly soluble in water and alcohol.

pH: 3.0 to 4.0 for 10 mg/mL solution.

Melting point: 250°C to 255°C (explosive decomposition).
Also reported as mp 205°C

Composition:

A sterile parenteral dosage form for reconstitution.

Each 600 mg vial contains 600 mg dacarbazine with 168.6 mg mannitol, 600 mg citric acid and sodium hydroxide or citric acid as pH adjuster.

Stability and Storage Recommendations

The recommended storage temperature for Dacarbazine for Injection BP is between 2°C and 8°C. Protect from light.

Preparation for Use and Reconstitution

To reconstitute:

600 mg vials: Add 59.1 mL of Sterile Water for Injection, USP.

The resulting solution contains an equivalent of 10 mg/mL of dacarbazine having a pH of 3.0 - 4.0. After reconstitution and prior to use, the solution in the vial may be stored between 2°C to 8°C for up to 24 hours or between 15°C to 25°C for up to 8 hours.

If the reconstituted solution is further diluted in 5% Dextrose Injection, USP or Sodium Chloride Injection, USP to concentrations ranging from 0.19 mg/mL – 3.0 mg/mL; the resulting solution may be stored between 2°C to 8°C for up to 24 hours.

Warning: Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, discolouration, or leakage should not be used. Discard unused portion.

Guidelines for Safe Use by Hospital Personnel

Handling

1. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
2. Personnel preparing Dacarbazine for Injection BP solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks.

Personnel regularly involved in the preparation and handling of antineoplastics should have bi-annual blood examinations.

Disposal

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.
2. All needles, syringes, vials, ampoules and other materials which have come in contact with Dacarbazine for Injection BP, should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.
3. If incineration is not available, dacarbazine may be detoxified by adding 5.5 parts by weight of calcium hypochlorite to each 1 part by weight of dacarbazine in 13 parts by weight of water. The

calcium hypochlorite should be added GRADUALLY and the procedure carried out with adequate ventilation since chlorine gas is liberated.

Vials

Prepare an adequate quantity of calcium hypochlorite solution (e.g.: Add 43.5 g calcium hypochlorite to 100 mL of water*). Withdraw any Dacarbazine for Injection BP remaining in the vial with the aid of a hypodermic syringe. Add to the prepared calcium hypochlorite solution slowly, preferably in chemical fume hood or biological safety cabinet - Class II. Add an appropriate quantity of the calcium hypochlorite solution to the vial to detoxify any remaining drug. Withdraw the solution and discard in the sewer system with running water. Dispose of the detoxified vials in a safe manner.

Needles, Syringes, Disposable and Non-Disposable Equipment

Rinse equipment with an appropriate quantity of calcium hypochlorite solution (43.5 g per 100 mL of water*).

Discard the solution in the sewer system with running water and discard disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

*Appropriate safety equipment such as goggles and gloves should be worn while working with calcium hypochlorite solution since it is corrosive.

Spillage/Contamination

Wear gloves, mask and protective clothing. Place spilled material in an appropriate container (i.e. cardboard for broken glass) and then in a polyethylene bag. Absorb remains with gauze pads or towels. Wash area with water and absorb with gauze or towels again and place in bag. Seal, double bag and mark as a hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean-up should wash with soap and water.

AVAILABILITY OF DOSAGE FORMS

Dacarbazine for Injection BP is available in 100 mL amber glass vial containing 600 mg of dacarbazine (single-use vials).

PHARMACOLOGY

Dacarbazine was initially selected for clinical trial on the basis of activity in the L1210 system. The studies did not suggest marked schedule dependency: alternative treatment schedules were not more effective than daily treatment. Dacarbazine appears to be non-cell stage specific, and in this respect dacarbazine is similar to l,3-Bis(2-chloroethyl)-l-nitrosourea(BCNU) and Nitrogen Mustard and dissimilar to methotrexate (MTX), cytarabine (Ara-C), 5-fluorouracil (5-FU) and vincristine (Vcr).

Kline has utilized a L1210 clone resistant to dacarbazine to demonstrate that sensitivity to TIC-Mustard, BCNU, CCNU, MTX, Ara-C and Cytoxan was retained. Wodinskyhas found that a strain of LI 210 resistant to 6MP retained sensitivity to dacarbazine. Kline demonstrated that LI 210 mice treated with optimal dosage of 5-FU and low dose dacarbazine have a greater survival than treated with either drug alone or a combination of low dose 5-FU and optimal dose MTX.

Dacarbazine has been shown to have a favourable effect against the B16 melanoma, the Lewis lung carcinoma and spontaneous AKR lymphoma in mice.

TOXICOLOGY

This triazeno (>N-N=N-) compound is markedly myelotoxic, at first to lymphocytic elements, secondly to thrombocytic and to myeloid elements and finally to erythroid elements. All systems are exposed to hemorrhagic injury when thrombocytopenia, leukopenia and anemia are so induced. At higher doses, dacarbazine is more toxic when administered intravenously than when administered orally.

The compound has been shown to be carcinogenic and teratogenic when ingested over a 14-week period in rats: no similar observations have been reported in other animals or in man.

The LD_{50} in the mouse approximates 250 mg/kg when given intravenously, 250-500 mg/kg intraperitoneally and greater than 1000 mg/kg when given orally. The LD_{50} in the rat is greater than 500 mg/kg by the intraperitoneal route, and greater than 1000 mg/kg by the oral route.

In dogs, oral administration of 5 mg/kg/day for 28 days produced no ill effects. At oral levels of 20 mg/kg/day for 7-15 days the expected failure of the hemopoetic system was observed and the dogs became moribund. The same was true at 200 mg/kg/day for 5-7 days, although the interval before death was shortened.

When the compound was given intravenously daily in dogs for 28 days, those receiving a dose of 2.5 mg/kg showed no changes other than perivenous haemorrhage and fibrosis at the injection site. At the 5 mg/kg level, there was a transient leukopenia, thrombocytopenia and elevation of the serum alkaline phosphatase, all of which reversed during continued administration of the drug or upon cessation of treatment. At the 10 mg/kg and 20 mg/kg levels, the same findings were present as those in the dogs given high dosage levels by the oral route.

Monkeys given 10 or 20 mg/kg/day orally for 28 days exhibited only a borderline thrombocytopenia at the higher level. One animal at 40 mg/kg/day for 13 days followed by 4 days at 60 mg/kg/day developed pulmonary edema with lymphoid depletion of the lymphoid tissues and terminal azotemia before sacrifice on day 21. One monkey given an oral dose of 60 mg/kg/day for 13 days demonstrated only reversible leukopenia and minimal erythropenia.

Intravenous administration in rhesus monkeys over 28 days at dosage levels of 15 mg/kg/day and 30 mg/kg/day produced changes only at the higher level. These changes were transient elevations of alkaline phosphatase and a leukopenia which reverted to normal following cessation of treatment. When the drug was given at a level of 60 mg/kg/day for 12 days and additional continuous or intermittent dosage at this level to a total of 20-28 doses, the changes expected from failure of the hemopoetic system occurred.

A clinical formulation of dacarbazine similar to Dacarbazine for Injection BP was injected intramuscularly in rabbits in volumes up to 0.5 ml in concentrations up to 2.5 mg/ml without gross or microscopic tissue changes. Acute subcutaneous injection of the same volumes and concentrations in the

guinea pig produced microscopic findings at the injection site of subcutaneous oedema, inflammation, fibrosis, focal necrosis and myositis in all concentrations including the control (water).

Twenty-four weanling rats were fed a powdered food containing 0.1 % of a clinical formulation of dacarbazine for one week followed by 0.05% for a further 13 weeks. A control group of the same size received the powdered food without dacarbazine. All were sacrificed at 18 weeks and submitted to gross autopsy with microscopic examination of various tissues. All 24 rats fed dacarbazine developed a variety of neoplasms; mammary carcinomas (an average of five/animal) and thymic lymphosarcomas were seen in all treated rats, lymphosarcoma in spleen, lymph nodes, and bone marrow were seen in 20,18, and 12 rats, respectively, and cerebral ependymomas and pulmonary alveolar carcinomas were seen in nine and four treated rats, respectively.

CLINICAL PHARMACOLOGY

Methodology of Assay:

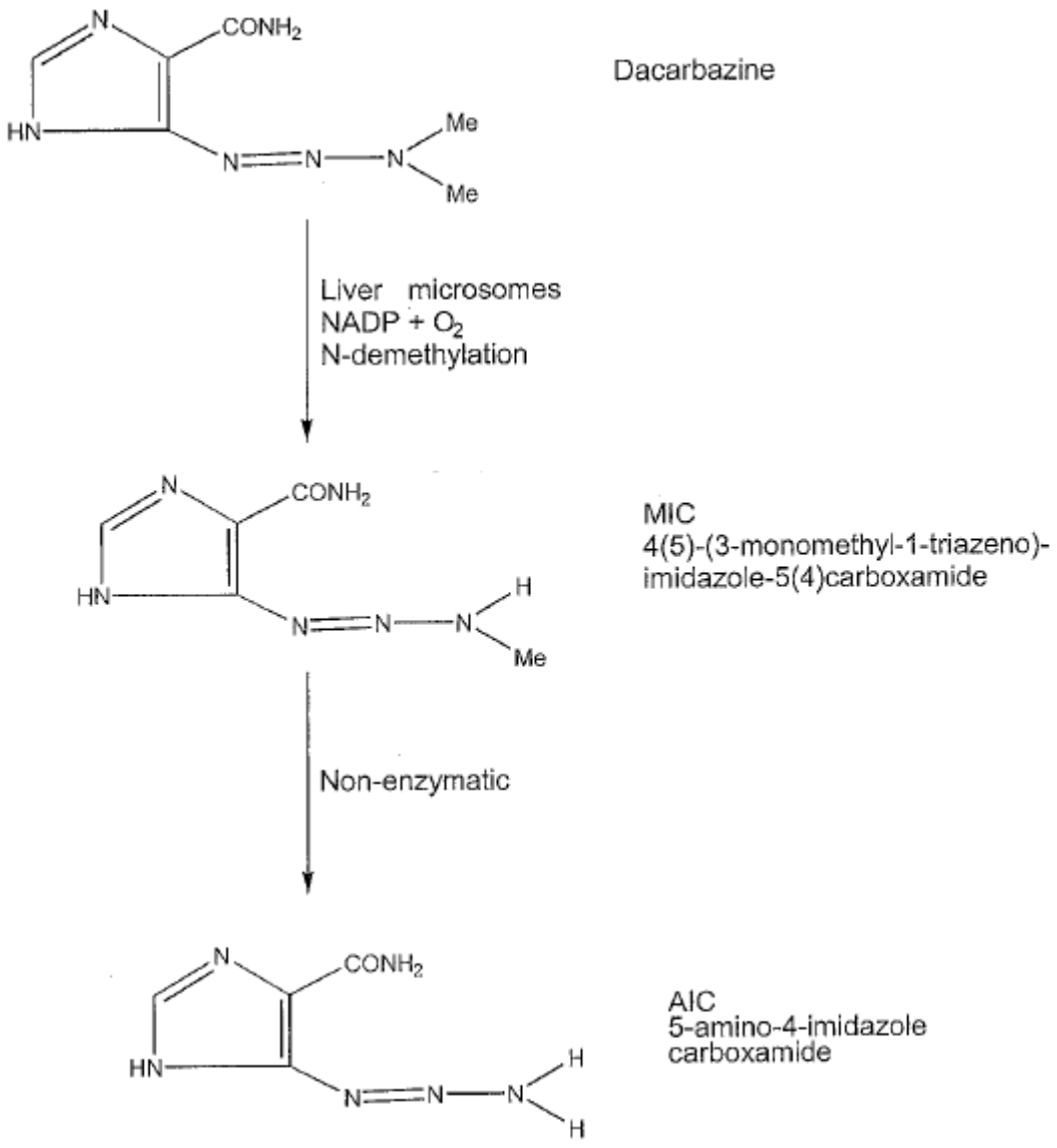
Loo and Stasswender (1967) developed a colorimetric method to measure dacarbazine in plasma and urine. The determination is based on the conversion of dacarbazine to a disodium compound on exposure to short wave ultraviolet light. Skibba et al. (1969) modified Loo's method by adding sulfosalicylic acid instead of TCA (as in Loo's original method). Skibba claimed his assay method provided a narrower range of standard deviations for the samples studied. Although some of the pharmacokinetic data below were generated using the above-mentioned methods, additional assay methods, including several different HPLC methods, have been developed since this time.[7,8]

Pharmacokinetics:

Dacarbazine is absorbed after oral administration, but toxicity and responses are reported to be erratic after this method of administration, and hence intravenous administration is used clinically. The volume of distribution exceeds the total body water, suggesting localisation in body tissue, probably the liver. Less than 5% of the drug is protein bound. Dacarbazine is metabolised primarily in the liver. N-demethylation results in the formation of methyltriazenoimidazole carboxamide. Further metabolism, involving the release of a carbonium ion, produces amino imidazole carboxamide (AIC) (See figure 1). 20-50% of the drug is reported to be excreted unchanged in the urine, with a further 12-24% excreted as

AIC. The majority of the urinary excretion occurs within the first 6-9 hours after intravenous administration. Renal clearance indicates net tubular secretion of the drug. At higher doses (>1200 mg/m^2), renal clearance may become saturated, and distribution and metabolism may also be saturated at this level.

Figure 1



Pharmacokinetic parameters of dacarbazine after intravenous administration in a variety of clinical settings are presented below.

Ref	Patients and dosage	Number of Patients	t ½α	t ½β	Vss	Clearance	
						L/kg/hr	L/hr/m^2
8	[a]850-1980 mg/m^2, 10-30 min infusion, cancer patients (various)	15	10.2	120		0.58	
13	[a]1000 mg/m^2, 24 hr infusion, melanoma patients		48	162	22.6 L/m^2		6.7
7	2.65-6.85 mg/kg iv bolus or 0.5-6 hr infusion, cancer patients (various)	8	2.9	41.4	0.632 L/kg	0.92[b]	
34	133-270 mg/m^2 iv bolus, cancer patients (various)	6		38			
40	4.5 mg/kg iv bolus, cancer patients (various)	6		75			

a) These doses are significantly larger than those used in current practice, and are not recommended.
b) reported as 15.4 mg/kg/min

In one patient with renal and hepatic dysfunction, the t ½α was 55 minutes, and the t ½β was 7.2 hours.

Dacarbazine in Malignant Melanoma:

Dacarbazine was selected for clinical trial on the basis of its activity against L1210 in mice. Extensive clinical studies have shown that dacarbazine is an effective chemotherapeutic agent in the treatment of malignant melanoma. Administered intravenously as a single agent in 1427 patients 81 patients had complete remission (CR) and 208 patients had partial remission (PR) with a total response (CR & PR) of 20.3 percent.

The largest single study was done by Central Oncology Group (CDE) in 682 patients of which 393 patients had malignant melanoma. The dose schedule was started at 0.5 mg/kg body weight and given daily for 10 days. The dose was gradually increased to a point where the hematologic toxicity became significant. Toxic effects from a daily dose 4.5 mg/kg for 10 days were considered acceptable and most of the patients were treated with this dose.

Twenty-one patients had complete remission and 88 patients had partial remission with a total response rate of 27.7 percent.

Acute Leukemia Cooperative Group B (ALB 6981) studied their patients on 2 dose schedules.

1. 300 mg/m^2/day for 6 consecutive days.
2. 100 mg/m^2/8 hourly for 6 consecutive days (total 18 doses).

Of the 28 patients studied on daily schedule, 2 patients had complete remission and 7 patients had partial remission with a total response rate of 32.1 percent. Twenty-two patients were studied on 8 hourly schedule, 1 patient had complete remission and 5 patients had partial remission with a total response rate of 27.3 percent. They concluded that there was no advantage of 8 hourly schedule over the daily injections.

Eastern Cooperative Oncology Group (EST 0868) studied *2* dosage schedules:

1. 2 mg/kg a day for 10 days.
2. 4.5 mg/kg a day for 10 days.

They studied 57 patients on schedule I. Six patients had complete remission and 13 patients had partial remission with a total response rate of 33 percent. Fifty-eight patients were studied on schedule 2. Thirteen patients had partial remission and none of the patients had complete remission. Response rate on this schedule was 22 percent. This would indicate that the low dose is as good as if not better than the higher dose.

Further studies by Eastern Cooperative Oncology Group were done with a dose of 150 mg/m^2/day for 5 days, Fifty-one patients were studied as in EST 0170 of which 3 patients had complete remission and 6 patients had partial remission with a total response of 17.6 percent. Seventy-one patients were studied as in EST 1071 of which 5 patients had complete remission and 8 patients had partial remission with a total response rate of 18.3 percent.

Southwest Cancer Chemotherapy Study Group (S WG 144) treated 110 patients with a dose of250 mg/m^2/day for 5 days schedule repeated at 3 week intervals.

Five patients had complete remission and 16 patients had partial remission with a total response rate of 19.1 percent.

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