PRODUCT MONOGRAPH

[Pr]MELPHALAN FOR INJECTION

Melphalan (as hydrochloride)

50 mg / vial

Sterile Lyophilized Powder

Professed

Antineoplastic (Alkylating) Agent

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9
Control Number: 193316

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50 mg / vial

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Intravenous Perfusion	Sterile Lyophilized Powder, 50 mg/vial	Hydrochloric acid, Povidone, Water for Injection Ethanol, Propylene glycol, Sodium citrate and Water for Injection

* For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING).

INDICATIONS AND CLINICAL USE

Melphalan for Injection (melphalan hydrochloride) is indicated for:

- the palliative treatment of multiple myeloma
- the palliation of nonresectable epithelial carcinoma of the ovary.
- Melphalan for Injection has been administered by hyperthermic isolated limb perfusion as an adjuvant to surgery in the treatment of malignant melanoma. However, there have been no prospective controlled or uncontrolled trials evaluating dose and its relationship to disease response and/or toxicity.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

- Melphalan for Injection (melphalan hydrochloride) should not be used in patients whose disease has demonstrated a prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be given the drug. There may be cross-sensitivity (skin rash) between melphalan and chlorambucil (LEUKERAN®).

- Melphalan for Injection should not be given if other similar chemotherapeutic agents or radiotherapy have been administered to the patient recently, or if neutrophil and/or platelet counts are depressed.

- Melphalan for Injection should not be administered concurrently with radiotherapy.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Melphalan for Injection (melphalan hydrochloride) should be administered in carefully adjusted dosages by or under the supervision of experienced physicians who are familiar with the drug's actions and the possible complications of its use.

The major acute toxicities associated with Melphalan for Injection are:

- Hypersensitivity reactions including anaphylaxis (See Immune)
- Bone marrow suppression (See Hematologic)
- Pulmonary toxicity (See Respiratory and OVERDOSAGE)
- Infertility (See Sexual Function / Reproduction)
- Secondary malignancies (See Carcinogenesis and Mutagenesis)

General

Melphalan for Injection should be administered in carefully adjusted dosages by or under the supervision of experienced physicians who are familiar with the drug's actions and the possible complications of its use. The drug should not be administered by hyperthermic isolated limb perfusion unless the clinician is experienced and well-trained in this technique.

In all instances where the use of Melphalan for Injection is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse events. Melphalan for Injection should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from previous cytotoxic therapy. Dose reduction should be considered in patients with renal insufficiency receiving IV Melphalan for Injection (See Hematologic and Renal).

Carcinogenesis and Mutagenesis

Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan hydrochloride). Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of acute leukemia, myeloproliferative syndrome or carcinoma is not possible. Published reports of leukemia in patients who have received melphalan hydrochloride (and other alkylating agents) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose. In one study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after melphalan hydrochloride therapy was 19.5% for cumulative doses ranging from 730 mg to 9652 mg. In this same study, as well as in an additional study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after melphalan hydrochloride therapy was less than 2% for cumulative doses under 600 mg. This does not mean that there is a cumulative dose below which there is no risk of the induction of secondary malignancy. The potential benefits from melphalan hydrochloride therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy.

Melphalan hydrochloride has been shown to cause chromatid or chromosome damage in man.

Hematologic

As with other nitrogen mustard drugs, excessive dosage will produce marked bone marrow suppression. Bone marrow suppression is the most significant toxicity associated with Melphalan for Injection in most patients. Therefore, the following tests should be performed at the start of therapy and prior to each subsequent dose of Melphalan for Injection: platelet count, hemoglobin, white blood cell count and differential. The occurrence of a platelet count below 50 x 10^9/L or an absolute neutrophil count below 0.5 x 10^9/L is an indication to withhold further therapy until the blood counts have sufficiently recovered. Frequent blood counts are essential to determine optimal dosage and to avoid toxicity.

If the leukocyte count falls below 3 x 10^9/L, or the platelet count below 100 x 10^9/L, the drug should be discontinued until the blood picture has had a chance to recover.

Blood counts may continue to fall for 6-8 weeks after initiation of treatment. So, at the first sign of abnormally large fall in leukocyte or platelet counts, treatment should be temporarily interrupted.

In one trial by Cornwell *et al.* (1982), melphalan hydrochloride administered intravenously without adjustment for renal failure increased incidence rates for severe leucopenia and thrombocytopenia by 35% in patients with renal insufficiency (BUN ≥ 30 mg/dL).

Immune

Acute hypersensitivity reactions, including anaphylaxis, have occurred infrequently (see ADVERSE REACTIONS). Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of volume expanders, pressor agents, corticosteroids, or antihistamines at the discretion of the physician.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Renal

Systemic exposure of melphalan hydrochloride was positively correlated to the degree of renal insufficiency following either route of administration. In one trial by Cornwell *et al.* (1982), increased incidence rate of bone marrow suppression has been associated with impaired renal function in patients with intravenous administration without dose adjustment for renal failure. Dose adjustments should be considered for patients with significant renal dysfunction (BUN ≥ 30mg/dL) and these patients should be closely monitored for toxicity.

Respiratory

Rare reports of pulmonary fibrosis or interstitial pneumonitis (including fatal reports) have been seen in patients treated with melphalan hydrochloride.

Sexual Function / Reproduction

Melphalan hydrochloride causes suppression of ovarian function in premenopausal women, resulting in amenorrhea in a significant number of patients.

Reversible and irreversible testicular suppression have also been reported. There is evidence from some animal studies that melphalan hydrochloride can have an adverse effect on spermatogenesis.

Special Populations

Pregnant Women: Safe use of melphalan hydrochloride has not been established with respect to adverse effects on fetal development. Therefore, it should be used in women of childbearing potential and particularly during early pregnancy only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from melphalan hydrochloride, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics: The safety and effectiveness in children have not been established.

Geriatrics: Clinical experience with melphalan hydrochloride has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Monitoring and Laboratory Tests

Periodic complete blood counts with differentials should be performed during the course of treatment with melphalan hydrochloride. At least one determination should be obtained prior to each dose. Patients should be observed closely for consequences of bone marrow suppression, which include severe infections, bleeding, and symptomatic anemia.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following information on adverse reactions is based on data from both oral and intravenous administration of melphalan hydrochloride as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication and dose received and also when given in combination with other therapeutic agents.

Gastrointestinal: Gastrointestinal effects such as nausea and vomiting occur in up to 50% of patients receiving intravenous doses of melphalan hydrochloride. Diarrhea is noted to occur one

week post high dose melphalan hydrochloride therapy. Oral ulceration and hepatic toxicity including veno-occlusive disease have been reported.

The incidence of diarrhea, vomiting and stomatitis becomes the dose-limiting toxicity in patients given high intravenous doses of melphalan hydrochloride in association with autologous bone marrow transplantation. Cyclophosphamide pretreatment appears to reduce the severity of gastrointestinal damage induced by high-dose melphalan hydrochloride and the literature should be consulted for details. Stomatitis at conventional doses is rare.

Hematologic: The most common side effect is bone marrow suppression leading to leukopenia, thrombocytopenia and anemia. Neutropenia and hemolytic anemia were also observed. Irreversible bone marrow failure has been reported. Bone marrow suppression is uncommon after limb perfusion.

Frequencies of severe myelosuppression and infections including fatal cases secondary to myelosuppression were much higher in patients with renal insufficiency (BUN $\geq$ 30mg/dL) than those with normal renal function who were treated with intravenous melphalan hydrochloride (See WARNINGS AND PRECAUTIONS, Renal).

Hepatic: Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported. Veno-occlusive disease has been reported following high-dose intravenous treatment.

Elevation in liver function enzymes is usually mild.

Hyperthermic Isolated Limb Perfusion: Adverse reactions may be attributable to the surgical procedure as well as the heated perfusion with Melphalan for Injection.

The local toxicity of hyperthermic perfusion appears to increase with increasing drug dose, duration of perfusion, and temperature. Muscle atrophy, muscle fibrosis, myalgia and increase in blood creatine phosphokinase were very commonly observed. Compartment syndrome has been commonly observed. Muscle necrosis and rhabdomyolysis have been seen at an unknown frequency. Severe nerve or muscle damage, severe skin or soft tissue reaction, or arterial thrombosis requiring amputation are rare, occurring in less than 1% of patients.

Systemic complications are uncommon, with reversible bone marrow suppression occurring in < 5% of patients. Wound complications, such as delayed healing or infection, occur in 5 to 10% of patients.

Hypersensitivity: Acute hypersensitivity reactions, including anaphylaxis, were reported in 2.4% of 425 patients receiving melphalan hydrochloride for myeloma (see WARNINGS AND PRECAUTIONS). These reactions were characterized by urticaria, pruritus, edema, skin rashes and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. Cardiac arrest had also been rarely reported in association with such events. These patients appeared to respond to antihistamine and corticosteroid therapy. Treatment with Melphalan for Injection should be discontinued if a hypersensitivity reaction occurs.

Local Reactions: Mild pain and/or irritation at, or near, the site of injection occurred after approximately half of the infusions, resolving within few hours after the end of the injection, without a need for treatment. Skin ulceration at injection site and flushing were reported as well as subjective and transient sensation of warmth and/or tingling.

Miscellaneous: Other reported adverse reactions include: skin hypersensitivity, vasculitis, alopecia, allergic reaction, pulmonary fibrosis, stomatitis, maculopapular rashes and interstitial pneumonitis. Fatal reports of pulmonary fibrosis have been received. Flushing sensations were reported at high doses of melphalan hydrochloride.

Renal: Temporary significant elevation of the blood urea has been seen in the early stages of melphalan hydrochloride therapy in myeloma patients with renal damage. An increase in creatinine levels has been observed.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1- Established or Potential Drug-Drug Interactions

Melphalan Hydrochloride	Effect	Clinical comment
Nalidixic acid	Hemorrhagic enterocolitis	Nalidixic acid together with high-dose intravenous melphalan hydrochloride has caused deaths in children due to hemorrhagic enterocolitis.
Cyclosporine	Impaired renal function	In bone marrow transplant patients who were conditioned with high-dose intravenous melphalan hydrochloride and who subsequently received cyclosporine to prevent graft-versus-host disease.
Live Viral Vaccines	Potential to cause infection in immunocompromised hosts	Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (See WARNINGS AND PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Recommended Dose

Intravenous

Multiple Myeloma:

The usual intravenous dose is 16 mg/m^2. Dosage reduction of up to 50% should be considered in patients with renal insufficiency (BUN ≥ 10.71 mmol/L [30 mg/dL]). The drug is administered in one dose and the length of infusion should be from 15 to 90 minutes. Melphalan is repeated at 2-week intervals initially for 4 doses, then at 4-week intervals after adequate recovery from toxicity. Available evidence suggests about one third to one-half of the patients with multiple myeloma show a favorable response to the drug. Experience with oral melphalan hydrochloride

suggests that repeated courses should be given since improvement may continue slowly over many months, and the maximum benefit may be missed if treatment is abandoned prematurely. Dose adjustment on the basis of blood cell counts at the nadir prior to each dose should be considered.

Perfusion Method
Malignant Melanoma:
Only physicians experienced and well-trained in hyperthermic isolated limb perfusion should administer the drug in this fashion.

Administration

Preparation for Administration / Stability:

Intravenous:

1. Reconstitute Melphalan for Injection, as directed, with 10 mL of the supplied diluent. This provides a 5 mg/mL solution of melphalan hydrochloride.

2. Immediately dilute the dose to be administered in 0.9% sodium chloride injection, USP, to a concentration not greater than 0.45 mg/mL.

3. Administer the diluted product over a minimum of 15 minutes.

4. Complete administration within 50 minutes of reconstitution.

5. Discard any reconstituted and diluted solutions remaining after 50 minutes of reconstitution.

The reconstituted product is stable for up to 2 hours at 30°C. A precipitate forms if the solution is stored at 5°C. **Do not refrigerate**.

Solutions diluted to a concentration of 0.1 mg/mL to 0.45 mg/mL in 0.9% sodium chloride injection are stable for up to 50 minutes at 30°C and 3 hours at 20ºC.

Reconstitution: Melphalan for Injection must be reconstituted, at room temperature, by rapidly transferring 10 mL of the supplied solvent-diluent directly into the vial of lyophilized powder using a sterile needle (20 gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution. The pH of resulting solution is approximately 6.5.

Vial Size	Volume of diluent to be added to vial	Approximate available volume	Nominal concentration per mL
50 mg	10 mL	10 mL	5 mg/mL

Melphalan for Injection solution has limited stability and should be prepared immediately before use. Any unused solution should be discarded. The reconstituted solution should be used

immediately and should not be refrigerated as this will cause precipitation. It is stable for up to 2 hours at 30°C.

Melphalan for Injection solution has reduced stability when further diluted in an infusion solution and the rate of degradation increases rapidly with rise in temperature. In that case, only sodium chloride infusion, 0.9% w/v should be used. Solutions diluted to a concentration of 0.1 mg/mL to 0.45 mg/mL in 0.9% sodium chloride infusion should be used immediately and are stable for up to 50 minutes at 30°C and 3 hours at 20°C.

Parenteral Products:
Parenteral drug products should usually be inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, do not use this product.

OVERDOSAGE

Overdose as high as 290 mg/m^2 resulting in death has been reported. It has also been reported that a pediatric patient survived a 254 mg/m^2 overdose treated with standard supportive care. The immediate effects are severe nausea and vomiting. Decreased consciousness, convulsions, muscular paralysis and cholinomimetic effects are less frequently seen. Severe mucositis, stomatitis, colitis, diarrhea, and hemorrhage of the gastrointestinal tract occur at high doses (>100 mg/m^2). Elevations in liver enzymes and veno-occlusive disease occur infrequently. Nephrotoxicity and adult respiratory distress syndrome have been reported rarely. The principal toxic effect is bone marrow suppression leading to leucopenia, thrombocytopenia and anemia. Hematologic parameters should be closely followed for 3 to 6 weeks. Administration of autologous bone marrow or hematopoietic growth factors (i.e., sargramostim, filgrastim) may shorten the period of pancytopenia. General supportive measures together with appropriate blood transfusions and antibiotics should be instituted as deemed necessary by the physician. This drug is not removed from plasma to any significant degree by hemodialysis or hemoperfusion.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Melphalan hydrochloride is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N^7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

Pharmacokinetics

Absorption
Mean (±SD) peak melphalan hydrochloride plasma concentrations in myeloma patients given melphalan hydrochloride intravenously at doses of 10 or 20 mg/m^2 were 1.2 ± 0.4 and 2.8 ± 1.9 µg/mL, respectively. Studies in children as young as 1 year showed results similar to adults.

Distribution

The steady-state volume of distribution of melphalan hydrochloride is 0.5 L/kg and approximates total body water. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan hydrochloride binding to plasma proteins is ranging from 69% to 78%. There is evidence that the protein binding is linear in the range of plasma concentrations usually achieved at standard dose therapy, but that the binding may become concentration-dependent at the concentrations observed at high dose therapy. Serum albumin is the major binding protein, accounting for about 55% to 60% of the plasma protein binding, and 20% is bound to ∝1-acid glycoprotein. In addition, melphalan hydrochloride binding studies have revealed the existence of an irreversible component attributable to the alkylation reaction with plasma proteins. Interactions with immunoglobulins have been found to be negligible.

Melphalan hydrochloride displays limited penetration of the blood-brain barrier. Melphalan hydrochloride was found at concentrations of approximately 10% of the corresponding plasma concentration in the cerebrospinal fluid samples following high-dose intravenous melphalan hydrochloride in two studies.

Metabolism
Melphalan hydrochloride is eliminated from plasma primarily by chemical hydrolysis to monohydroxy and dihydroxy-melphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in man.

Elimination
Following injection, drug plasma concentrations declined rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 70 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7 to 9 mL/min/kg (250 to 325 mL/min/m^2) were observed.

Melphalan hydrochloride clearance may be decreased in renal impairment. An increase in AUC (i.e. melphalan hydrochloride systemic exposure) was observed in patients with renal impairment when melphalan hydrochloride was administered by either route. One study noted an increase in the occurrence of severe leukopenia in patients with elevated BUN after 10 weeks of therapy (see WARNINGS AND PRECAUTIONS, Hematologic).

The pharmacokinetics of melphalan hydrochloride administered by closed circuit limb perfusion have been studied by several investigators. Melphalan hydrochloride concentrations declined rapidly and biexponentially from circulating perfusate with average terminal half-lives reported from 26 min (n=4) to 53 min (n=48). Systemic exposure to melphalan hydrochloride during limb perfusion is generally very low. Peak melphalan hydrochloride concentrations in the closed circuit perfusate are typically 10 to 100 times greater than peak concentrations in plasma observed following standard dose systemic intravenous therapy for multiple myeloma.

STORAGE AND STABILITY

Dry Powder: Store at controlled room temperature (15°C – 30°C). Protect from light.

Diluted solution: Stable up to 50 minutes at 30°C and 3 hours at 20ºC.

Reconstituted Solution: Stable up to 2 hours at 30°C.

SPECIAL HANDLING INSTRUCTIONS

As with other toxic compounds, caution should be exercised when handling and preparing the solution of melphalan hydrochloride. Skin reactions associated with accidental exposure may occur. The use of gloves is recommended. If the solution of melphalan hydrochloride contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MELPHALAN FOR INJECTION (lyophilized) 50 mg:
Vial of 50 mg melphalan (as hydrochloride).

Solvent-diluent for Melphalan for Injection:
Vial of 10 mL.

Each MELPHALAN FOR INJECTION vial contains the equivalent of 50 mg of melphalan, in the form of the hydrochloride, as a sterile, clear colorless to slight brownish color, lyophilized cake or powder and povidone, 20 mg.

Each vial of solvent-diluent provides 10 mL of buffer solution containing sodium citrate 0.20 g, ethanol 0.52 mL, propylene glycol 6.00 mL, and water for injection, q.s.

MELPHALAN FOR INJECTION is supplied as a 2-component pack which contains one vial of lyophilized powder and a single vial of solvent diluent.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

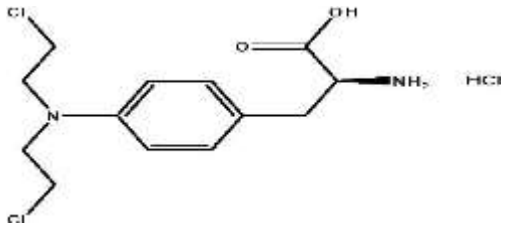
Common name: Melphalan Hydrochloride

Chemical name:

1. 4-Bis(2-chloroethyl)amino-L-phenylalanine hydrochloride;
2. p-di(2-chloroethyl)amino-L-phenylalanine hydrochloride

Molecular formula and molecular mass: $C_{13}H_{19}Cl_3N_2O_2$, 314.66 g/mol

Structural formula:



Physicochemical properties:

Physical description: White to almost-white powder.

pKa: pKa (strongest acidic) 1.29
pKa (strongest basic) 9.51

Solubility of Melphalan: Practically insoluble in water. It dissolves in diluted mineral acids.

Therapeutic Category: Antineoplastic Agent

DETAILED PHARMACOLOGY

Metabolism

***In vivo* Studies**

Alberts et al. found that plasma melphalan levels are highly variable after oral dosing, both with respect to the time of the first appearance of melphalan in plasma and to the peak concentrations achieved. Whether this results from incomplete gastrointestinal absorption or a variable "first pass" hepatic metabolism is unknown. Five patients were studied after both oral and intravenous dosing with 0.6 mg/kg as a single bolus dose by each route. The areas under the plasma concentration-time curves after oral administration averaged 61 ± 26% (± standard deviation; range 25-89%) of those following intravenous administration. In 10 patients given a single, oral dose of 0.6 mg/kg of melphalan, the terminal plasma half-disappearance time of parent drug was 101 ± 63 minutes. The 24-hour urinary excretion of parent drug in these patients was 10 ± 6%, suggesting that renal clearance is not a major route of elimination of parent drug.

Tattersall et al. using universally labelled ^{14}C-melphalan, found substantially less radioactivity in the urine of those given it intravenously (35-65% in 7 days). Following either oral or intravenous administration, the pattern of label recovery was similar, with the majority being recovered in the first 24 hours. Following oral administration, peak radioactivity occurred in plasma at 2 hours and then disappeared with a half-life of approximately 160 hours. In one patient where parent drug (rather than just radiolabel) was determined, the melphalan half-disappearance time was 67 minutes.

***In vitro* Studies - Protein Binding and Dialysis**

After incubating ^{14}C-Melphalan in human plasma at 37°C for 8 hours, Chang et al. found that only 70% of the carbon-14 label was removed by methanol extraction. Almost none of the methanol-extractable ^{14}C-Melphalan was in the form of parent drug at that time.

Equilibrium dialysis of ^{14}C-Melphalan in human plasma at 37°C (30 μg of melphalan per mL plasma) against 0.05 M phosphate buffer, pH 7.4, demonstrated that 30% of the carbon-14 remained undialyzable after equilibrium had been reached at 8 hours. These observations may indicate alkylation of plasma proteins by melphalan.

MICROBIOLOGY

Not available.

TOXICOLOGY

Animals

Species	LD_{50}
Mouse	21 mg/kg P.O.
Mouse	10 mg/kg I.P.
Rat	4 mg/kg I.P.

No information is available on the acute effects of melphalan hydrochloride. However, chronic administration (by I.P. injection) produced lymphosarcomas and dose-related increase in lung tumours in mice and peritoneal tumours in rats.

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PART III: CONSUMER INFORMATION

PrMELPHALAN FOR INJECTION

This leaflet is part III of a three-part "Product Monograph" published for Melphalan for Injection, approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Melphalan for Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Melphalan for Injection (melphalan hydrochloride) is indicated:

- to relieve symptoms caused by multiple myeloma (a form of cancer that affects plasma cells produced in the bone marrow).
- to relieve symptoms caused by nonresectable epithelial carcinoma of the ovary (cancer that begins in the cells of the ovary).

What it does:
Melphalan for Injection belongs to a group of chemotherapy drugs called antineoplastic alkylating agents. Melphalan for Injection interferes with the growth of cancer cells which eventually are killed. Normal cells may also be affected which may lead to side effects.

When it should not be used:
Do not take Melphalan for Injection if:

- You are allergic to melphalan hydrochloride or chlorambucil.
- You are allergic to any ingredients of the drug or any component of the container.
- Your disease has not responded to Melphalan for Injection treatment.
- You are currently receiving or have recently received radiotherapy or chemotherapy.
- You have been recently treated with medicines similar to Melphalan for Injection.
- You have low neutrophil or platelet count (neutrophil and platelets are blood cells).

What the medicinal ingredient is:
The medicinal ingredient for Melphalan for Injection is Melphalan hydrochloride.

What the important nonmedicinal ingredients are:
Melphalan for Injection: Povidone, hydrochloric acid and water for injection.
Each vial contains 10 mL buffer solution contains the following important non-medicinal ingredients: sodium citrate 0.20g, ethanol 0.52 mL, propylene glycol 6.00 mL, and water for injection.

What dosage forms it comes in:
Melphalan for Injection is available as a 50 mg / vial.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Only take this drug as prescribed by a qualified doctor.
- Melphalan for Injection can lower your blood counts. Your blood counts should be measured regularly.
- Melphalan for Injection may cause an allergic reaction.
- Melphalan for Injection may cause abdominal upset and may harm your lungs.
- Melphalan for Injection may harm an unborn fetus.
- Melphalan for Injection may cause secondary cancers.

BEFORE you use Melphalan for Injection talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in Melphalan for Injection.
- you are pregnant or likely to become pregnant.
- you are breastfeeding a baby.
- you have been vaccinated, or planning to be vaccinated with a live vaccine.
- you are currently receiving, or have recently had radiotherapy or chemotherapy.
- you have kidney disease.

Melphalan for Injection has been reported to cause cancers in some patients who have been treated with the drug.

If you need surgery, tell the doctor/anaesthetist that you are taking Melphalan for Injection.

INTERACTIONS WITH THIS MEDICATION

It is important that your doctor know about all your medication so that you get the best possible treatment. Tell your doctor about all the medicines you are taking including those you have bought yourself. Nalidixic acid or cyclosporine should not be taken while you are taking, or soon after taking Melphalan for Injection.

Vaccination with live organism vaccines is not recommended.

PROPER USE OF THIS MEDICATION

You will receive this medicine under a doctor's care. It is infused through your blood.

Ask your doctor or pharmacist if you have any questions about how it is being given to you or what your dose is.

As with other toxic compounds, caution should be exercised when handling and preparing the solution of Melphalan for Injection.

Usual dose:
The dosage is very variable and it may be changed from time to time by your doctor. If you have any questions, ask your doctor or pharmacist.

From time to time while you are taking Melphalan for Injection, your doctor will want you to have a blood test. This is to check your blood cell count and to change your dose if necessary.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Melphalan for Injection may cause side-effects in some people.

Production of bone marrow cells may be reduced.

In women, periods may stop.

In men, sperm production may be reduced or stopped.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking Melphalan for Injection, **Stop** taking the medicine and tell your doctor immediately:
- sudden wheeziness, difficulty breathing, chest pain or chest tightness.
- swelling of eyelids, face, lips, mouth or tongue.
- lumpy skin rash or "hives" anywhere on the body.

Tell your doctor if any of the following happen to you while you are taking Melphalan for Injection:
- if you feel sick, lose your appetite, have diarrhoea or vomit.
- if you develop mouth ulcers, a skin rash and/or itching.
- effects on the blood may occur. Your doctor will do regular blood tests, but you should tell him at once if you notice any signs of fever or infection, or any unexpected bruising or bleeding.
- if you notice any signs of jaundice (yellowing of the whites of the eyes or the skin) as this may be due to hepatitis (inflammation/infection of the liver). If you have any blood tests to check how your liver is working, this medicine may affect the results.
- if you notice that you are gradually becoming more breathless than usual.
- you may notice some hair loss, especially if you are on a high dose of Melphalan for Injection.

Tell your pharmacist or doctor if you notice any other symptoms that you do not understand which are not mentioned here.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Side Effect/ Symptom	Your Doctor or Pharmacist	Stop taking drug and call your doctor or pharmacist immediately
Very Common	Any sign of fever or infection, or any unexpected bruising or bleeding	X	
Rare	Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate		X
	Jaundice (yellowing of the whites of eyes or the skin)	X	
	Progressively increasing shortness of breath	X	

This is not a complete list of side effects. For any unexpected effects while taking Melphalan for Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Melphalan for Injection (powder or cake) should be stored at a controlled room temperature 15°C - 30°C. Protect from light. Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Apotex Inc. at 1-800-667-4708 or visit the www.apotex.ca.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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