PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTARO-MELPHALAN

Melphalan Injection

Powder for solution for injection, 50 mg/vial, for Intravenous and intra-arterial use

Taro Std.

Antineoplastic (Alkylating) Agent

Taro Pharmaceuticals Inc.
130 East Drive,
Brampton, Ontario
Canada L6T 1C1

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.2 Recommended Dose and dose Adjustment	07/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TARO-MELPHALAN (melphalan) is indicated for:

- the palliative treatment of multiple myeloma
- the palliation of nonresectable epithelial carcinoma of the ovary.
- TARO-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.

1.1 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years): TARO-MELPHALAN is approved for use in the geriatric population. However, dosing precautions apply (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

TARO-MELPHALAN is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.
- 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.
- Patients who have recently been administered other similar chemotherapeutic agents or radiotherapy, or if neutrophil and/or platelet counts are depressed (see 7 WARNINGS and PRECAUTIONS, Hematologic).
- Patients who are receiving radiotherapy.
- Women who are breast-feeding (see 7.1.2 Breast-feeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

TARO-MELPHALAN (melphalan) 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 are:

- Hypersensitivity reactions including anaphylaxis (See 7 Immune)
- Bone marrow suppression (See 7 Hematologic)
- Pulmonary toxicity (See 7 Respiratory and 5 OVERDOSAGE)
- Infertility (See 7 Reproduction)
- Secondary malignancies (See 7 Carcinogenesis and Mutagenesis)
- Mutagenicity and teratogenicity (See 7 Carcinogenesis and Mutagenesis)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Due to the risk of thromboembolism, the decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (See 7 Hematologic).

4.2 Recommended Dose and Dosage Adjustment

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 suggests t hat 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.

Intra-arterial/Hyperthermic isolated limb Perfusion

Malignant Melanoma:

Only physicians experienced and well-trained in hyperthermic isolated limb perfusion should administer the drug in this fashion. Based on the recent literature, the usual doses of melphalan is 13 mg/L or 1.0 mg/kg in the upper limb and 10 mg/L or 1.5 mg/kg in the lower limb added to the perfusate. Perfusion lasts for approximately 60 minutes under mild hyperthermic conditions (final tissue temperatures, 39° to 41° C).

Pediatrics (< 18 years): Health Canada has not authorized an indication for pediatric use.
Geriatrics (> 65 years): 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.

4.3 Reconstitution

TARO-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 seconds) until a clear solution is obtained. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution.

The resulting solution contains the equivalent of 5 mg per mL anhydrous melphalan and has a pH of approximately 6.5.

Table 1 – Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
50 mg	10 mL	10 mL	5 mg/mL

TARO-MELPHALAN 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.

TARO-MELPHALAN 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.

4.4 Administration

Preparation for Administration/Stability:

Intravenous:

1. Reconstitute TARO-MELPHALAN for injection, as directed, with 10 mL of the supplied diluent. This provides a 5 mg/mL solution of melphalan.
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.

4.5 Missed Dose

Missed/omitted doses should not be made up at the end of the cycle.

5 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous and intra-arterial Perfusion	Injection/ 50 mg/vial	Ethanol, hydrochloric acid (for pH control), povidone, propylene glycol, sodium citrate, water for injection.

TARO-MELPHALAN (melphalan) for injection (freeze-dried) 50 mg:

Vial of 50 mg melphalan as the hydrochloride. TARO-MELPHALAN for injection is supplied as a 2-component pack comprising a vial containing a freeze-dried powder and a vial of solvent-diluent. The stopper is not made with natural rubber latex.

Each TARO-MELPHALAN vial contains the equivalent of 50 mg of melphalan, in the form of the hydrochloride, as a sterile, white to off-white, freeze-dried powder, 20 mg of providone, and 0.051 mL of hydrochloric acid (for pH control).

Solvent-diluent for TARO-MELPHALAN for injection:
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.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

TARO-MELPHALAN 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 TARO-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 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 (See 7 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) especially in elderly patients after long combination therapy and radiotherapy. 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 (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 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 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 therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy notably if melphalan is used in combination with thalidomide or lenalidomide and prednisone considering increase leukaemogenic risk. Melphalan in combination with lenalidomide and prednisone and, to a lesser extent, thalidomide and prednisone has been also associated with the increased risk of solid second primary malignancy (SPM) in elderly newly diagnosed multiple myeloma patients.

Patient characteristics (e.g. age, ethnicity), primary indication and treatment modalities (e.g. radiation therapy, transplantation), as well as environmental risk factors (e.g., tobacco use) should be evaluated prior to melphalan administration. Doctors must examine the patient by usual measurements to ensure the early detection of cancer and initiate treatment if necessary.

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

Driving and Operating Machinery

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Bone marrow suppression : As with other nitrogen mustard drugs, excessive dosage will produce marked bone marrow suppression. Bone marrow suppression is the most significant toxicity associated with TARO-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 TARO-MELPHALAN: 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 administered intravenously without adjustment for renal failure increased incidence rates for severe leucopenia and thrombocytopenia by 35% in patients with renal insufficiency (BUN $\geq$ 30mg/dL).

Venous Thromboembolism: Melphalan in combination with lenalidomide and prednisone or in combination with thalidomide and prednisone or dexamethasone is associated with an increased risk of venous thromboembolism. Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be restarted at the original dose dependent upon a benefit -risk assessment. The patient should continue anticoagulation therapy during the course of melphalan treatment.

Immune

Acute hypersensitivity reactions, including anaphylaxis, have occurred infrequently (See 8 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.

Monitoring and Laboratory Tests

Periodic complete blood counts with differentials should be performed during the course of treatment with melphalan. 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.

Renal

Systemic exposure of melphalan 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.

Reproductive Health : Female and Male Potential

Due to an increased risk of venous thromboembolism in patients undergoing treatment with melphalan in combination with lenalidomide and prednisone or in combination with thalidomide and prednisone or dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, her partner should switch to a barrier method like condom. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. Considering that Melphalan has been shown to cause chromatid or chromosome damage in man, it is recommended that men who are receiving treatment with Melphalan not father a child during treatment and up to 6 months afterwards.

- **Fertility**

  Melphalan 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 can have an adverse effect on spermatogenesis. It is recommended that men have a consultation on sperm preservation before treatment due to the possibility of irreversible infertility as a result of Melphalan treatment.

Respiratory

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

7.1 Special Populations

7.1.1 Pregnant Women

Safe use of melphalan 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.

7.1.2 Breast-feeding

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, 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 (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (< 18 years): The safety and effectiveness in children have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Clinical experience with TARO-MELPHALAN 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following information on adverse reactions is based on data from both oral and intravenous administration of melphalan 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 30% of patients receiving conventional oral doses of melphalan and in up to 50% of patients receiving intravenous doses of melphalan. Diarrhea is noted to occur one week post high dose melphalan 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 in association with autologous bone marrow transplantation. Cyclophosphamide pretreatment appears to reduce the severity of gastrointestinal dam age induced by high-dose melphalan 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 ≥ 30mg/dL) than those with normal renal function who were treated with intravenous melphalan (See 7 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 for injection for myeloma (See 7 Immune). 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 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.

Neoplasms benign, malignant and unspecified (including cysts and polyps): Secondary acute myeloid leukaemia and myelodysplastic syndrome.

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

Reproductive system and breast disorders: Includes azoospermia and amenorrhoea

Vascular disorders: Deep vein thrombosis and pulmonary embolism

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Drug-Behavioural interactions have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Effect	Clinical comment
Nalidixic acid	Hemorrhagic enterocolitis	Nalidixic acid together with high-dose intravenous melphalan 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 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 7 WARNINGS AND PRECAUTIONS).
Busulfan	Potential to influence the development of toxicities in pediatric population	In pediatric populations, for the Busulfan-Melphalan regimen it has been reported that the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.

9.5 Drug-Food Interactions

The oral administration of melphalan tablets immediately after food delayed the time to achieving peak plasma concentrations and reduced the area under the plasma concentration-time curves by between 39 and 54% (see 10 CLINICAL PHARMACOLOGY).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

TARO-MELPHALAN (melphalan) 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 N7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

10.3 Pharmacokinetics

Absorption

The absorption of oral melphalan is highly variable with respect to both the time to first appearance of the drug in plasma and peak plasma concentration. In studies of the absolute bioavailability of melphalan the mean absolute bioavailability ranged from 56 to 85%.

Mean (±SD) peak melphalan plasma concentrations in myeloma patients given melphalan intravenously at doses of 10 or 20 mg/m2 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.

The oral administration of melphalan tablets immediately after food delayed the time to achieving peak plasma concentrations and reduced the area under the plasma concentration-time curves by between 39 and 54% (see 9 DRUG INTERACTIONS).

Distribution:

The steady-state volume of distribution of melphalan is 0.5 L/kg and approximates total body water. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan 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 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 displays limited penetration of the blood-brain barrier. Melphalan was found at concentrations of approximately 10% of the corresponding plasma concentration in the cerebrospinal fluid samples following high-dose intravenous melphalan in two studies.

Metabolism:

Melphalan 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.

***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.

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/m2) were observed.

Melphalan clearance may be decreased in renal impairment. An increase in AUC (i.e. melphalan systemic exposure) was observed in patients with renal impairment when melphalan 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 7 Hematologic).

The pharmacokinetics of melphalan administered by closed circuit limb perfusion have been studied by several investigators. Melphalan 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 during limb perfusion is generally very low. Peak melphalan 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.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

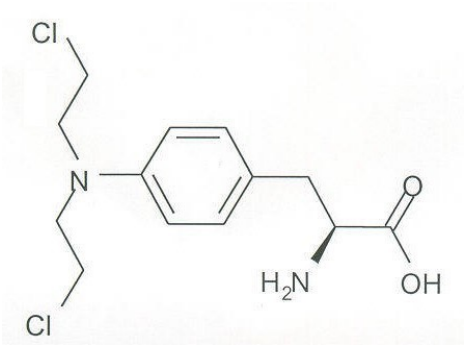
Drug Substance

Proper name: melphalan

Chemical name: 4-[bis(2-chloroethyl)amino]-L-Phenylalanine

Molecular formula and molecular mass: $C_{13}H_{18}Cl_2N_2O_2$, 305.20

Structural formula:



Physicochemical properties: A white to cream-coloured powder which melts with decomposition at about 175°C. Soluble in ethanol and propylene glycol. Practically insoluble in water.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

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. However, chronic administration (by I.P. injection) produced lymphosarcomas and dose -related increase in lung tumours in mice and peritoneal tumours in rats.

Reproductive and Developmental Toxicology :

In mice, melphalan administered intraperitoneally at a dose of 7.5 mg/kg, showed reproductive effects

attributable to cytotoxicity in specific male germ cell stages and induced dominant lethal mutations and heritable translocations in post-meiotic germ cells, particularly in mid to late stage spermatids.

A study was performed to measure the total reproductive capacity of melphalan in female mice. Females received a single intraperitoneal dose of 7.5 mg/kg melphalan and were then housed with an untreated male for most of their reproductive life span (a minimum of 347 days post -treatment). A pronounced reduction in litter size occurred within the first post -treatment interval, followed by an almost complete recovery. Thereafter, a gradual decline in litter size occurred. This was simultaneous with a reduction in the proportion of productive females, a finding associated with an induced reduction in the number of small follicles.

17 SUPPORTING PRODUCT MONOGRAPHS

[Pr]ALKERAN® (powder for solution, 50 mg / vial), Submission Control 261646, Product Monograph, Aspen Pharmacare Canada Inc. SEP 23, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTARO-MELPHALAN

melphalan injection

Read this carefully before you start taking TARO-MELPHALAN and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TARO-MELPHALAN.

Serious Warnings and Precautions

TARO-MELPHALAN should only be prescribed by a healthcare professional experienced in the use of anti-cancer drugs.

The following serious side effects have been seen in patients taking TARO-MELPHALAN:

- **Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, fast heartbeat.
- **Bone Marrow Suppression:** signs and symptoms of infections (including fever, chills, sore throat, mouth ulcers), fatigue, easy bruising, bleeding of the nose, gums or mouth, tiny red spots on the skin, rash, shortness of breath, pale skin lips and nail beds.
- **Lung Problems Causing Death:** suddenly worsening shortness of breath, wheezing, tiredness, possibly with a cough or fever, painful breathing.
- **Infertility in both men and women.**
- **Birth defects in babies whose mother or father was taking TARO-MELPHALAN.**
- **Development of new cancers, other than the cancer you are being treated for.**

What is TARO-MELPHALAN® used for?

TARO-MELPHALAN is indicated used in adults:

- to relieve symptoms caused by multiple myeloma, a cancer of the blood
- to relieve symptoms caused by a type of ovarian cancer (epithelial carcinoma of the ovary) that cannot be removed by surgery
- together with surgery to treat skin cancer (malignant melanoma)

How does TARO-MELPHALAN work?

TARO-MELPHALAN belongs to a group of anti-cancer medicines called antineoplastic alkylating agents. These medications work by stopping cancer cells from dividing and growing.

What are the ingredients in TARO-MELPHALAN injection:

Medicinal ingredient: melphalan.

Non-medicinal ingredients: ethanol, hydrochloric acid (for pH control), povidone, propylene glycol, sodium citrate, water for injection.

TARO-MELPHALAN comes in the following dosage forms:

Injection (freeze-dried): 50 mg/vial

Do not use TARO-MELPHALAN if:

- you are allergic to melphalan, chlorambucil or any of the other ingredients in TARO-MELPHALAN.
- your disease has not responded to TARO-MELPHALAN treatment.
- you are currently receiving or have recently received radiotherapy or chemotherapy.
- you have been recently treated with medicines similar to TARO-MELPHALAN.
- you have low neutrophil or platelet counts (neutrophils and platelets are blood cells).
- you are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TARO-MELPHALAN. Talk about any health conditions or problems you may have, including if you:

- are pregnant or likely to become pregnant.
- have recently been vaccinated, or are planning to be vaccinated with a live vaccine.
- have kidney disease.

Other warnings you should know about:

TARO-MELPHALAN has been reported to cause new cancers in some patients who have been treated with the drug. If you have any concerns or notice any new symptoms talk to your healthcare professional.

If you need surgery, tell the healthcare professional or anaesthetist that you are taking TARO-MELPHALAN.

Your healthcare professional will do blood tests before you start treatment with TARO-MELPHALAN and before each dose.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TARO-MELPHALAN:

- nalidixic acid, an antibiotic used to treat bacterial infections.
- cyclosporine, used to prevent organ rejection in people who have had an organ transplant.
- busulfan
- vaccination with live vaccines.

How to take TARO-MELPHALAN injection:

TARO-MELPHALAN injection will be given to you by a specially trained doctor or nurse. They will use one of the two methods:

- with a needle directly into a vein (IV),
  or
- Into an artery (intra-arterial perfusion)

Usual adult dose:

Your healthcare professional will decide on your dose based on your weight and height. Your dose may change based on how well you are responding to treatment and your blood test results.

Thromboembolic events

You should receive prophylaxis of venous thromboembolism for at least the first 5 months of treatment especially if you have additional thrombotic risk factors. Your doctor will dec ide what measures should be taken after careful assessment of your underlying risk factors.

If you experience any thromboembolic event, tell your doctor immediately as your treatment must be discontinued and a standard anticoagulation therapy started. Your doctor will decide if you should restart melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone once the thromboembolic events have been managed. You should continue anticoagulation therapy during the course of melphalan treatment.

Overdose:

If you think you, or a person you are caring for, have been given too much TARO-MELPHALAN contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss an appointment to receive a dose of TARO-MELPHALAN contact your healthcare professional as soon as possible.

What are possible side effects from using TARO-MELPHALAN?

These are not all the possible side affects you may feel when taking TARO-MELPHALAN. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- In women, periods may stop
- In men, sperm production may be reduced or stopped
- Nausea, vomiting, diarrhea
- Mouth ulcers or sores
- Hair loss
- Skin rash and/or itching
- Mild pain and/or irritation where TARO-MELPHALAN was injected
- Flushing, feelings of warmth and/or tingling
- Muscle pain, wasting, or scarring

TARO-MELPHALAN can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Bone Marrow Suppression: signs and symptoms of infections (including fever, chills, sore throat, mouth ulcers), fatigue, easy bruising, bleeding of the nose, gums or mouth, tiny red spots on the skin, rash, shortness of breath, pale skin lips and nail beds		X	
COMMON			
Compartment Syndrome: pain, pale skin, numbness, tingling and weakness or paralysis in the leg or arm where TARO-MELPHALAN was injected		X	
RARE			
Allergic Reaction: swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, rash, hives, fast heartbeat			X
Liver Problems: yellowing of the whites of eyes or the skin, dark urine, abdominal pain, nausea, vomiting, loss of appetite		X	
Lung Problems (interstitial lung disease, pneumonitis): fatal and serious with suddenly worsening shortness of			X

breath, wheezing, tiredness, possibly with a cough or fever, painful breathing			
Injection Site Reaction: severe muscle or nerve damage, pain, redness, inflammation, tenderness, ulcers or infection at the injection site that can lead to amputation			X
NOT KNOWN			
Severe Muscle Breakdown (rhabdomyolysis): muscle weakness, fatigue, soreness, bruising, fever, passing little or no urine, tea-coloured urine			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- TARO-MELPHALAN injection should be stored at controlled room temperature (15° -30°C).
- Protect from light.
- Keep out of reach and sight of children.

If you want more information about TARO-MELPHALAN:

- Talk to your healthcare professional
- You may want to read this leaflet again. **Please Do Not Throw It Away** until you have finished your medicine.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.taro.ca, or by calling 1-800-268-1975.

This leaflet was prepared by: Taro Pharmaceuticals Inc.

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