SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Melphalan Tablets USP 2 mg and 5 mg
Brand name: MELPTIZ 2

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 2 mg of the active ingredient Melphalan
Each film coated tablet contains 5 mg of the active ingredient Melphalan
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Melphalan Tablets are indicated in the treatment of multiple myeloma and advanced ovarian adenocarcinoma.
Melphalan either alone or in combination with other drugs has a significant therapeutic effect in a proportion of patients suffering from advanced breast carcinoma.
Melphalan is effective in the treatment of a proportion of patients suffering from polycythaemia vera.

4.2 Posology and Method of Administration

Since Melphalan is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary.
Oral administration in Adults: The absorption of Melphalan after oral administration is variable. Dosage may need to be cautiously increased until myelosuppresion is seen, in order to ensure that potentially therapeutic levels have been reached.
Multiple Myeloma: Numerous regimes have been used and the scientific literature should be consulted for details. The administration of Melphalan and prednisone is more effective than Melphalan alone. The combination is usually given on an intermittent basis, although the superiority of this technique over continuous therapy is not established. A typical oral dosage schedule is 0.15 mg/kg bodyweight/day in divided doses for 4 days repeated at intervals of six weeks. Prolonging treatment beyond one year in responders does not appear to improve results.
Ovarian adenocarcinoma: A typical regimen is 0.2 mg/kg bodyweight/day orally for 5 days. This is repeated every 4-8 weeks, or as soon as the bone marrow has recovered. Melphalan has also been used intravenously in the treatment of ovarian carcinoma.
Advanced carcinoma of the breast: Melphalan has been given orally at a dose of 0.15 mg/kg bodyweight or 6 mg/m^2 body surface area/day for 5 days and repeated every 6 weeks. The dose was decreased if bone marrow toxicity was observed.
Polycythaemia vera: For remission induction the usual dose is 6-10 mg daily for 5-7 days, after which 2-4 mg daily is given until satisfactory disease control is achieved.

Therapy is maintained with a dose of 2-6 mg per week. During maintenance therapy, careful haematological control is essential with dosage adjustment according to the results of frequent blood counts.
Children: Melphalan is very rarely indicated in children and dosage guidelines cannot be stated.
Use in the elderly: There is no specific information available on the use of Melphalan in elderly patients.
Dosage in renal impairment: In patients with moderate to severe renal impairment currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering the oral preparation to these patients, but it may be prudent to use a reduced dose initially.

4.3 Contraindications

Melphalan should not be given to patients who have suffered a previous hypersensitivity reaction to melphalan.

4.4 Special Warnings and Precautions for use

Melphalan is an active cytotoxic agent for use only under the direction of physicians experienced in the administration of such agents.
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: Since Melphalan is a potent myelosuppresive agent, it is essential that careful attention should be paid to the monitoring of blood counts to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia. Blood counts may continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in leucocyte or platelet counts, treatment should be temporarily interrupted. Melphalan should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.
Renal impairment: Patients with renal impairment should be closely observed as they may have uraemic marrow suppression.
Mutagenicity: Melphalan is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the drug.
Carcinogenicity: The evidence is growing that melphalan in common with other alkylating agents has been reported to be leukaemogenic. There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloid, malignant melanoma, macroglobulinaemia, cold agglutinin syndrome and ovarian cancer.
A comparison of patients with ovarian cancer who received alkylating agents with those who did not, showed that the use of alkylating agents, including melphalan, significantly increased the incidence of acute leukaemia. The leukaemogenic risk must be balanced against the potential therapeutic benefit when considering the use of melphalan.
Melphalan causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients.

4.5 Interaction with other Medicinal Products and other Forms of Interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals.
Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic enterocolitis.
Impaired renal function has been described in bone marrow transplant patients who were pre-conditioned with high dose intravenous melphalan and who subsequently received ciclosporin to prevent graft-versus-host disease.

4.6 Pregnancy and Lactation

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving Melphalan.
Teratogenicity: The teratogenic potential of Melphalan has not been studied. In view of its mutagenic properties and structural similarity to known teratogenic compounds, it is possible that melphalan could cause congenital defects in the offspring of patients treated with the drug.
Pregnancy: The use of melphalan should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.
Lactation: Mother receiving Melphalan should not breast-feed.

4.7 Effects on Ability to Drive And use Machines

No information on the effects of Melphalan on the ability to drive and use machines is available.

4.8 Undesirable Effects

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.
The following convention has been utilised for the classification of frequency:- Very common ≥1/10, common ≥1/100, <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

Blood and Lymphatic System Disorders

Very common: bone marrow depression leading to leucopenia, thrombocytopenia and anaemia

Rare: haemolytic anaemia

Immune System Disorders

Rare: allergic reactions

Allergic reactions to melphalan such as urticaria, oedema, skin rashes and anaphylactic shock have been reported uncommonly following initial or subsequent dosing, particularly after intravenous administration. Cardiac arrest has also been reported rarely in association with such events.

Respiratory, Thoracic and Mediastinal Disorders

Rare: interstitial pneumonitis and pulmonary fibrosis (including fatal reports)

Gastrointestinal Disorders

Very common: nausea, vomiting and diarrhoea; stomatitis at high dose

Rare: stomatitis at conventional dose

Gastrointestinal effects such as nausea and vomiting have been reported in up to 30% of patients receiving conventional oral doses of melphalan.

Hepatobiliary Disorders

Rare: hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice

Skin and Subcutaneous Tissue Disorders

Very common: alopecia at high dose

Common: alopecia at conventional dose

Rare: maculopapular rashes and pruritus

Renal and Urinary Disorders

Common: temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage

4.9 Overdose

Symptoms and signs: Gastro-intestinal effects, including nausea, vomiting and diarrhoea are the most likely signs of acute oral overdosage. Diarrhoea, sometimes haemorrhagic, has been reported after intravenous overdosage. The principal toxic effect is bone marrow aplasia, leading to leucopoenia, thrombocytopenia and anaemia.

Treatment: There is no specific antidote. The blood picture should be closely monitored for at least four weeks following overdosage until there is evidence of recovery.
General supportive measures, together with appropriate blood transfusion, should be instituted if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Melphalan is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis-2-chlorethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking two DNA strands and thereby preventing cell replication.

5.2 Pharmacokinetic Properties

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%.
Intravenous administration can be used to avoid variability in absorption associated with myeloablative treatment.
In a study of 18 patients administered melphalan 0.2 to 0.25 mg/kg bodyweight orally, a maximum plasma concentration (range 87 to 350 nanograms/ml) was reached within 0.5 to 2.0 h.
The 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 45%.
Distribution: Melphalan displays limited penetration of the blood-brain barrier. Several investigators have sampled cerebrospinal fluid and found no measurable drug. Low concentrations (~10% of that in plasma) were observed in a single high-dose study in children.
Elimination: In 13 patients given oral melphalan at 0.6 mg/kg bodyweight, the plasma mean terminal elimination half-life was 90 ± 57 min with 11% of the drug being recovered in the urine over 24 h.
In 18 patients administered melphalan 0.2 to 0.25 mg/kg bodyweight orally, the mean elimination half-life was 1.12 ± 0.15 h.
Special Patient Populations
• **Renal impairment:** Melphalan clearance may be decreased in renal impairment.
• **Elderly:** No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life.

5.3 Preclinical Safety Data
There are no preclinical data of relevance to the prescriber, which are additional to that in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Microcrystalline cellulose PH102
Colloidal silicon dioxide
Crospovidone
Magnesium stearate
Opadry White (03B580006)
Purified water

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store in a refrigerator (2°C-8°C)

6.5 Nature and contents of container

25 Tablets in a HDPE Container.

6.6 Special precautions for disposal and other handling

Safe handling of melphalan tablets: The handling of Melphalan tablets should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations and/or regulations (for example Royal Pharmaceutical Society of Great Britain Working Party on the Handling of Cytotoxic Drugs).
Provided the outer coating of the tablet is intact, there is no risk in handling Melphalan tablets.
Melphalan tablets should not be divided.
Disposal: Melphalan tablets should be destroyed in accordance with relevant local regulatory requirements concerning the disposal of cytotoxic drugs.

7. MARKETING AUTHORISATION HOLDER

Tizig Pharma Pvt Ltd

Factory ward no # 1,

Banepa, Kathmandu, Nepal

8. MARKETING AUTHORISATION NUMBER(S)

Not Applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

Dec 2021

11. DOSIMETRY

Not Applicable