

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alkeran Tablets 2 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg melphalan.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, round, biconvex film-coated tablets, one side engraved with an "A" and the other side engraved "GX EH3".

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of multiple myeloma and advanced ovarian adenocarcinoma.

4.2 Posology and method of administration

Since Alkeran is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary (see section 4.4).

Posology

Multiple myeloma

A typical oral dosage schedule is 0.15 mg/kg bodyweight/day in divided doses for 4 days repeated at intervals of six weeks. Numerous regimens have, however, been used and the scientific literature should be consulted for details.

The administration of oral Alkeran and prednisone may be more effective than Alkeran alone. The combination is usually given on an intermittent basis.

Prolonging treatment beyond one year in responders does not appear to improve results.

Advanced ovarian adenocarcinoma

A typical regimen is 0.2 mg/kg bodyweight/day given orally in divided doses for 5 days. This is repeated every 4 to 8 weeks, or as soon as the bone marrow has recovered.

Paediatric population

Alkeran is only rarely indicated in the paediatric population and absolute dosage guidelines cannot be provided.

Older people

Although Alkeran is frequently used at conventional dosage in the older people, there is no specific information available relating to its administration to this patient sub-group. However, caution should be taken where there is renal impairment.

Renal impairment

Alkeran clearance, though variable, may be decreased in renal impairment (see section 4.4).

Currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering Alkeran Tablets to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established.

Method of administration

Oral administration in adults: The absorption of Alkeran after oral administration is variable. Dosage may need to be cautiously increased until myelosuppression is seen, in order to ensure that potentially therapeutic levels have been reached.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Lactation.

4.4 Special warnings and precautions for use

ALKERAN IS AN ACTIVE CYTOTOXIC AGENT FOR USE 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 individuals. Therefore, immunisations with live organism vaccines are not recommended.

Monitoring

Bone marrow depression, with leucopenia and thrombocytopenia, is the main side effect. The time of maximum depression is variable, and 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 leukocyte or platelet counts treatment should be temporarily interrupted.

Alkeran should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

Venous thromboembolic events

Patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone, have an increased risk of deep vein thrombosis and pulmonary embolism (see section 4.8). The risk appears to be greatest during the first 5 months of therapy, especially in patients with additional thrombotic risk factors (e.g. smoking, hypertension, hyperlipidaemia and history of thrombosis). These patients should be closely monitored and actions to minimize all modifiable risk factors should be undertaken. Thromboprophylaxis and dosing/anticoagulation therapy recommendations are provided in section 4.2.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. If a patient experiences any thromboembolic events, discontinue the treatment immediately and initiate the standard anticoagulation therapy. 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 throughout the course of treatment.

Neutropenia and thrombocytopenia

Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving combination drug regimens described (section 4.8).

Mutagenicity

Melphalan has been shown to be mutagenic and carcinogenic in animals and chromosome aberrations have been observed in patients being treated with the drug. Melphalan has also been shown to be carcinogenic in animals (section 5.3), and the possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

Carcinogenicity (second primary malignancy)

Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS)

Alkeran, in common with other alkylating agents has been reported to be leukaemogenic, especially in older patients after long combination therapy and radiotherapy.

There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloidosis, malignant melanoma, multiple myeloma, macroglobulinaemia, cold agglutinin syndrome and there has been a significant increase in patients with 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.

Before the start of the treatment, the leukaemogenic risk (AML and MDS) must be balanced against the potential therapeutic benefit, especially if the use of melphalan in combination with thalidomide or lenalidomide and prednisone is considered, as it has been shown that these combinations may increase the leukaemogenic risk. Before, during and after treatment doctors must therefore examine the patient at all times by usual measurements to ensure the early detection of cancer and initiate treatment if necessary.

Solid tumours

Use of alkylating agents has been linked with the development of second primary malignancy (SPM). In particular, melphalan in combination with lenalidomide and prednisone and, to a lesser extent, thalidomide and prednisone has been associated with the increased risk of solid 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.

Contraception

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, she should switch to another reliable contraceptive method (i.e. ovulation inhibitory progesterone-only pills such as desogestrel, barrier method, etc). The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception.

Renal impairment

Alkeran clearance may be reduced in patients with renal impairment, who may also have uraemic bone marrow suppression. Dose reduction may therefore be necessary (see section 4.2), and these patients should be closely observed.

Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.

4.5 Interaction with other medicinal products and other forms of interactions

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4).

Nalidixic acid together with high-dose intravenous melphalan has caused deaths in the paediatric population due to haemorrhagic enterocolitis.

In paediatric population, 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.

Impaired renal function has been described in bone marrow transplant patients who were pre-conditioned with high dose intravenous melphalan and who subsequently received cyclosporin to prevent graft-versus-host disease.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of melphalan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). 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.

Alkeran should not be used during pregnancy and particularly during the first trimester, unless considered absolutely essential by the physician. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be practised when either partner is receiving Alkeran.

Breast-feeding

Mothers receiving Alkeran should not breastfeed (see section 4.3).

Fertility

Alkeran causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients.

There is evidence from some animal studies that Alkeran can have an adverse effect on spermatogenesis (see section 5.3). Therefore, it is possible that Alkeran may cause temporary or permanent sterility in male patients.

It is recommended that men who are receiving treatment with melphalan not father a child during treatment and up to 6 months afterwards and that they have a consultation on sperm preservation before treatment due to the possibility of irreversible infertility as a result of melphalan treatment.

4.7 Effects on ability to drive and use machines

Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied.

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 $\geq 1/10$, common $\geq 1/100$, $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10,000$ and $< 1/1000$, very rare $< 1/10,000$, not known (cannot be estimated from the available data).

Body System	Frequency	Side effects
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	secondary acute myeloid leukaemia and myelodysplastic syndrome (see section 4.4).
Blood and Lymphatic System Disorders	Very common	bone marrow depression leading to leucopenia, thrombocytopenia, neutropenia ¹ and anaemia.
	Rare	haemolytic anaemia.
Immune System Disorders	Rare	hypersensitivity ² (see Skin and Subcutaneous Tissue Disorders).
Respiratory, Thoracic and Mediastinal Disorders	Rare	interstitial lung disease and pulmonary fibrosis (including fatal reports).
Gastrointestinal Disorders	Very common	nausea ³ , vomiting ³ and diarrhoea; stomatitis at high dose.
	Rare	stomatitis at conventional dose.
Hepatobiliary Disorders	Rare	liver 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	rash maculo-papular and pruritus (see Immune System Disorders).
Renal and Urinary Disorders	Common	blood urea increased ⁴
Vascular Disorders ⁵	Not known	deep vein thrombosis and pulmonary embolism
Reproductive system and breast disorders	Not known	azoospermia, amenorrhoea.
General Disorders and Administration Site Conditions	Very common	pyrexia

1. Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone (see sections 4.4).
2. 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.
3. Gastrointestinal effects such as nausea and vomiting have been reported in up to 30% of patients receiving conventional oral doses of melphalan.
4. Temporary significant elevation of the blood urea has been commonly seen in the early stages of melphalan therapy in myeloma patients with renal damage.
5. The clinically important adverse reactions associated with the use of melphalan in combination with thalidomide and prednisone or dexamethasone and to a lesser extent melphalan with lenalidomide and prednisone include: deep vein thrombosis and pulmonary embolism (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il>

In addition, you can report to Padagis via the following address: [Padagis.co.il](https://padagis.co.il)

4.9 Overdose

Symptoms and signs

Gastro-intestinal effects, including nausea, vomiting and diarrhoea are the most likely early signs of acute oral overdosage. The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia.

Treatment

General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary and consideration given to hospitalisation cover with anti-infective agents, and the use of haematological growth factors.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, alkylating agents, nitrogen mustard analogues, ATC code: L01AA03.

Mechanism of action

Melphalan is a bifunctional alkylating anti-neoplastic agent with some immunosuppressant properties. Formation of carbonium intermediates from each of the two bis-2-chloroethyl 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 54%.

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 paediatrics.

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 (see section 4.2 and 4.4).

Elderly

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life (see section 4.2).

5.3 Preclinical safety data

Mutagenicity

Melphalan is mutagenic in animals.

Reproductive toxicity

Reproduction studies in rats treated with oral doses of 0.81-2.42 times the Maximum Recommended Human Dose (MRHD) revealed embryo-lethal and teratogenic effects. Congenital anomalies included those of the brain (underdevelopment, deformation, meningocele, and encephalocele), eye (anophthalmia and microphthalmos), reduction of the mandible and tail, and hepatocele (see section 4.6).

Fertility Studies

In mice, melphalan at clinically relevant exposure levels 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.

Females received melphalan at clinically relevant exposure levels and were then housed with an untreated male for most of their reproductive life span. 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 (see section 4.6).

Genotoxicity

Melphalan has been tested for genotoxicity in a number of short-term assays, both *in vitro* and *in vivo*. In mice, oral administration of melphalan at a dose of 0.81 times the MRHD increased frequencies of dominant lethal mutations, chromosomal aberrations, sister chromatid exchange, micronuclei and DNA strand breaks.

The observed mutations originated primarily from large deletions in the postspermatogonial cells whereas other types of mutagenic mechanisms predominated in the spermatogonial cells.

This *in vivo* data is supported by *in vitro* studies showing that cell culture treatment with melphalan (at concentrations ranging from 0.1 to 25 μ M) also induced DNA damage.

In addition, it induced aneuploidy and sex-linked recessive lethal mutations in *Drosophila*, and mutation in bacteria. It was positive with all strains in the Ames test at concentrations of 200 μ g/plate and above. The mutagenic activity of melphalan was increased 3-fold in the presence of liver S9 metabolising preparations, which is unexpected since melphalan is not considered to need liver activation to produce a cytotoxic effect.

Carcinogenicity

Melphalan is a direct-acting alkylating agent that is carcinogenic via a genotoxic mechanism, which is sufficiently supported by animal studies.

Development of neoplastic tumours in mice reported following oral administration of melphalan at doses of 0.10-1.63 times the MRHD; in monkeys, the carcinogenic potential was observed at a dose of 0.16 times the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Opadry White YS-1-18097-A (Hypromellose, Titanium Dioxide, Macrogol)

Crospovidone

Magnesium stearate

Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening: 60 days

6.4 Special precautions for storage

Store in a refrigerator 2°C to 8°C.

6.5 Nature and contents of container

Alkeran Tablets are supplied in amber glass bottles of 25 tablets with a child-resistant closure.

6.6 Special precautions for disposal and other handling

The handling of Alkeran formulations should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations.

Pregnant Staff should not handle cytotoxics. Protective clothing, including gloves, should be worn.

Alkeran Tablets should not be divided.

Provided the outer coating of the tablet is intact, there is no risk in handling Alkeran Tablets.

Disposal

Alkeran Tablets should be destroyed in accordance with relevant local regulatory requirements concerning the disposal of cytotoxic drugs.

Adequate care should be taken in the disposal of waste material, including containers and any other contaminated material.

7 MANUFACTURER

Excella GmbH & Co. KG., Feucht, Germany, for Aspen.

8 REGISTRATION HOLDER

Padagis Israel Agencies Ltd., 1 Rakefet St., Shoham, Israel.

9 REGISTRATION NUMBER

129-55-30948-00

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10.11.22