Summary of Product Characteristics

1. Name of the medicinal product

Myleran Tablets 2 mg

2. Qualitative and quantitative composition

Each 2 mg tablet contains 2 mg of the active substance busulfan.

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated tablet

Myleran tablets 2 mg are white, film-coated, round biconvex tablets engraved "GX EF3" on one side and "M" on the other.

4. Clinical particulars

4.1 Therapeutic Indications

For the palliative treatment of chronic granulocytic leukaemia (also called chronic myeloid leukaemia).

4.2 Posology and method of administration

General

The bioavailability of oral Busulfan shows large intra-individual variations ranging from 47% to 103% (mean 80%) in adults and from 22% to 120% (mean 68%) in children (see section 5.2).

There are other formulations available which may be more suitable for paediatric patients.

Myleran tablets are usually given in courses or administered continuously. The dose must be adjusted for the individual patient under close clinical and haematological control. Should a patient require an average daily dose of less than the content of the available Myleran tablets, this can be achieved by introducing one or more busulfan free days between treatment days. The tablets should not be divided (see section 6.6*).*

Obese

Dosing based on body surface area or adjusted ideal body weight should be considered in the obese (see section 5.2).
The relevant literature should be consulted for full details of treatment schedules.

Chronic granulocytic leukaemia (also called chronic myeloid leukaemia):

Induction in adults

Treatment is usually initiated as soon as the condition is diagnosed. The dose is 0.06 mg/kg/day, with an initial daily maximum of 4 mg, which may be given as a single dose.

There is individual variation in the response to Myleran and in a small proportion of patients the bone marrow may be extremely sensitive (see section 4.4*).*

The blood count must be monitored at least weekly during the induction phase and it may be helpful to plot counts on semilog graph paper.

The dose should be increased only if the response is inadequate after three weeks.

Treatment should be continued until the total leucocyte count has fallen to between 15 and 25 x 10^9 per litre (typically 12 to 20 weeks). Treatment may then be interrupted, following which a further fall in the leucocyte count may occur over the next two weeks. Continued treatment at the induction dose after this point or following depression of the platelet count to below 100 x 10^9 per litre is associated with a significant risk of prolonged and possibly irreversible bone marrow aplasia.

Maintenance in adults

Control of the leukaemia may be achieved for long periods without further Myleran treatment; further courses are usually given when the leucocyte count rises to 50 x 10^9 per litre, or symptoms return.

Some clinicians prefer to give continuous maintenance therapy. Continuous treatment is more practical when the duration of unmaintained remissions is short.

The aim is to maintain a leucocyte count of 10 to 15 x 10^9 per litre and blood counts must be performed at least every 4 weeks. The usual maintenance dosage is on average 0.5 to 2 mg/day, but individual requirements may be much less. Should a patient require an average daily dose of less than the content of one tablet, the maintenance dose may be adjusted by introducing one or more Myleran free days between treatment days.

NOTE: Lower doses of Busulphan should be used if it is administered in conjunction with other cytotoxic agents (see section 4.5 and 4.8).

Paediatric population

Chronic granulocytic leukaemia is very rare in the paediatric age group. Myleran may be used to treat Philadelphia chromosome positive (Ph' positive) disease, but the Ph' negative juvenile variant responds poorly.

4.3 Contraindications

Myleran should not be used in patients whose disease has demonstrated resistance to busulfan.

Myleran should not be given to patients who have previously suffered a hypersensitivity to the active substance busulfan or to any of the excipients listed in section 6.1.

Mothers receiving Myleran should not breast-feed their infants.

4.4 Special warnings and precautions for use

Busulfan 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.

Myleran should be discontinued if lung toxicity develops (see section 4.8*).*

Myleran should not generally be given in conjunction with or soon after radiotherapy.

Myleran is ineffective once blast transformation has occurred.

If anaesthesia is required in patients with possible pulmonary toxicity, the concentration of inspired oxygen should be kept as low as safely as possible and careful attention given to post-operative respiratory care.

Hyperuricaemia and/or hyperuricosuria are not uncommon in patients with chronic granulocytic leukaemia and should be corrected before starting treatment with Myleran. During treatment, hyperuricaemia and the risk of uric acid nephropathy should be prevented by adequate prophylaxis, including adequate hydration and the use of allopurinol.

Studies in renally impaired patients have not been conducted, however, as busulfan is moderately excreted in the urine, dose modification is not recommended in these patients. However, caution is recommended.

Busulfan has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolized through the liver, caution should be observed when busulfan is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment.

The medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Conventional dose Treatment

Patients who are concurrently treated with the conventional dose of busulfan and itraconazole or metronidazole should be closely monitored for signs of busulfan toxicity. At concomitant use of these agents with busulfan weekly blood counts are recommended (see section 4.5).

Monitoring

Careful attention must be paid to monitoring the blood counts throughout treatment to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia (see section 4.8).

Hepatic veno-occlusive disease is a major complication that can occur during treatment with Myleran. Patients who have received prior radiation therapy, for three or more cycles of chemotherapy, or prior progenitor cell transplant may be at an increased risk of developing hepatic veno-occlusive disease (see section 4.8).

Safe Handling of Myleran Tablets

See section 6.6.
Myleran is genotoxic in non-clinical studies (see section 5.3).

Mutagenicity

Various chromosome aberrations have been noted in cells from patients receiving busulfan.

Carcinogenicity

On the basis of human studies, Myleran was considered by the International Agency for Research on cancer to show sufficient evidence for carcinogenicity. The World Health Association has concluded that there is a causal relationship between Myleran exposure and cancer.

Widespread epithelial dysplasia has been observed in patients treated with long-term Myleran, with some of the changes resembling precancerous lesions.

A number of malignant tumours have been reported in patients who have received Myleran treatment.

The evidence is growing that Myleran, in common with other alkylating agents, is leukaemogenic. In a controlled prospective study in which 2 years' Myleran treatment was given as an adjuvant to surgery for lung cancer, long-term follow-up showed an increased incidence of acute leukaemia compared with the placebo-treated group. The incidence of solid tumours was not increased.

Although acute leukaemia is probably part of the natural history of polycythaemia vera, prolonged alkylating agent therapy may increase the incidence.

4.5 Interaction with other medicinal products and other forms of interaction

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

The effects of other cytotoxics producing pulmonary toxicity may be additive.

The administration of phenytoin to patients receiving high-dose Myleran may result in a decrease in the myeloblative effect.

In patients receiving high-dose busulfan it has been reported that co-administration of itraconazole decreases clearance of busulfan by approximately 20% with corresponding increases in plasma busulfan levels. In combination with metronidazole (1200 mg, given as 400 mg three times daily) busulfan values are increased in approximately 80% (see section 4.4). Fluconazole had no effect on busulfan clearance. Consequently, high-dose Myleran in combination with itraconazole or metronidazole is reported to be associated with an increased risk of busulfan toxicity (see section 4.4).

A reduced incidence of hepatic veno-occlusive disease and other regimen-related toxicities have been observed in patients treated with high-dose Myleran and cyclophosphamide when the first dose of cyclophosphamide has been delayed for >24 hours after the last dose of busulfan.

Paracetamol is described to decrease glutathione levels in blood and tissues, and may therefore decrease busulfan clearance when used in combination.

Increases in busulfan exposure have been observed at concomitant administration of busulfan and deferasirox. The mechanism behind the interaction is not fully elucidated. It is recommended to regularly monitor busulfan plasma concentrations and, if necessary, adjust the busulfan dose in patients who are or have recently been treated with deferasirox.

4.6 Fertility, pregnancy and lactation

Fertility

Busulfan can lead to suppression of ovarian function and amenorrhoea in women and suppression of spermatogenesis in men (see section 4.8 and 5.3).

Pregnancy

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

The use of Myleran should be avoided during pregnancy whenever possible. In animal studies (see section 5.3) it has the potential for teratogenic effects, whilst exposure during the latter half of pregnancy resulted in impairment of fertility in offspring. In every individual case the expected benefit of treatment to the mother must be weighed against the possible risk to the foetus.

A few cases of congenital abnormalities, not necessarily attributable to busulfan, have been reported and third trimester exposure may be associated with impaired intra-uterine growth. However, there have also been many reported cases of apparently normal children born after exposure to Myleran in utero, even during the first trimester.

Breastfeeding

It is not known whether Myleran or its metabolites are excreted in human breast milk. Mothers receiving Myleran should not breast-feed their infants.

4.7 Effects on ability to drive and use machines

There are no data on the effect of Myleran on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the drug.

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

The following table of adverse reactions originated from the use of busulfan, or busulfan in combination with other therapeutic agents.

System organ class	Frequency	Side effects
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Leukaemia secondary to oncology chemotherapy (see section 4.4)

System organ class	Frequency	Side effects
Blood and lymphatic system disorders *	Very common	Dose-related bone marrow failure, manifesting as leukopenia and particularly thrombocytopenia
	Rare	Aplastic anaemia
Nervous system disorders	Rare	At high-dose: convulsion (see section 4.4 and 4.5)
	Very rare	Myasthenia gravis
Eye disorders	Rare	Lens disorder and cataract (which may be bilateral) corneal thinning (reported after bone marrow transplantation preceded by high-dose Myleran treatment)
Cardiac disorders	Common	At high-dose: cardiac tamponade in patients with thalassaemia
Respiratory, thoracic and mediastinal disorders *	Very common	At high-dose: idiopathic pneumonia syndrome
	Common	Interstitial lung disease following long term conventional dose use
Gastrointestinal disorders	Very common	At high-dose: nausea, vomiting, diarrhoea, mouth ulceration
	Rare	At conventional dose: nausea, vomiting, diarrhoea, mouth ulceration, which may possibly be ameliorated by using divided doses. Dry mouth
	Not known	Tooth hypoplasia
Hepatobiliary disorders *	Very common	At-high-dose: hyperbilirubinaemia, jaundice, venoocclusive liver disease (see section 4.4 and 4.5) and biliary fibrosis with hepatic atrophy and necrosis
	Rare	Jaundice and abnormal hepatic function, at conventional dose. Biliary fibrosis
Skin and subcutaneous tissue disorders *	Common	Alopecia at high-dose. Skin hyperpigmentation (see also General disorders and administration site conditions)
	Rare	Alopecia at conventional dose, skin reactions including urticaria, erythema multiforme, erythema nodosum, porphyrianon-acute, rash, dry skin and fragility of the skin with complete anhydrosis cheilosis, Sjögren's syndrome. An increased radiation skin injury in patients receiving radiotherapy soon after high-dose Myleran

System organ class	Frequency	Side effects
Renal and urinary disorders	Common	At high-dose: in combination with cyclophosphamide cystitis haemorrhagic
Reproductive system and breast disorders *	Very common	Ovarian disorder and amenorrhoea with menopausal symptoms in pre-menopausal patients at high-dose; severe and persistent ovarian failure, including failure to achieve puberty after administration to young girls and pre-adolescents at high-dose. Male infertility, azoospermia and testicular atrophy in male patients receiving Myleran
	Uncommon	Ovarian disorder and amenorrhoea with menopausal symptoms in pre-menopausal patients at conventional dose. In very rare cases, recovery of ovarian function has been reported with continuing treatment
	Very rare	Gynaecomastia
General disorders and administration site conditions *	Rare	Dysplasia

* Description of selected adverse events

Blood and lymphatic system disorders

Aplastic anaemia (sometimes irreversible) has been reported rarely, typically following long-term conventional doses and also high doses of Myleran.

Respiratory, thoracic and mediastinal disorders

Pulmonary toxicity after either high or conventional dose treatment typically presents with non-specific non-productive cough, dyspnoea and hypoxia with evidence of abnormal pulmonary physiology. Other cytotoxic agents may cause additive lung toxicity (see section 4.5). It is possible that subsequent radiotherapy can augment subclinical lung injury caused by busulfan. Once pulmonary toxicity is established the prognosis is poor despite busulfan withdrawal and there is little evidence that corticosteroids are helpful.

Idiopathic pneumonia syndrome is a non-infectious diffuse pneumonia which usually occurs within three months of high-dose Myleran conditioning prior to allogeneic or autologous haemopoietic transplant. Diffuse alveolar haemorrhage may also be detected in some cases after broncholavage. Chest X-rays or CT scans show diffuse or non-specific focal infiltrates and biopsy shows interstitial pneumonitis and diffuse alveolar damage and sometimes fibrosis.

Interstitial pneumonitis may occur following conventional dose use and lead to pulmonary fibrosis. This usually occurs after prolonged treatment over a number of years. The onset is usually insidious but may also be acute. Histological features include atypical changes of the alveolar and bronchiolar epithelium and the presence of giant cells with large hyperchromatic nuclei. The lung pathology may be complicated by superimposed infections. Pulmonary ossification and dystrophic calcification have also been reported.

Hepatobiliary disorders

Busulfan is not generally considered to be significantly hepatotoxic at normal therapeutic doses. However, retrospective review of postmortem reports of patients who had been treated with low-dose busulfan for at least two years for chronic granulocytic leukaemia showed evidence of centrilobular sinusoidal fibrosis.

Skin and subcutaneous tissue disorders

Hyperpigmentation occurs, particularly in those with a dark complexion. It is often most marked on the neck, upper trunk, nipples, abdomen and palmar creases. This may also occur as part of a clinical syndrome (see General disorders and administration site conditions*).*

Reproductive system and breast disorders

Studies of busulfan treatment in animals have shown reproductive toxicity (see Section 5.3).

General disorders and administration site conditions

Clinical syndrome (weakness, severe fatigue, anorexia, weight loss, nausea and vomiting and hyperpigmentation of the skin) resembling adrenal insufficiency (Addison's disease) but without biochemical evidence of adrenal suppression, mucous membrane hyperpigmentation or hair loss (see Skin and subcutaneous tissue disorders) has been seen in a few cases following prolonged Myleran therapy. The syndrome has sometimes resolved when busulfan has been withdrawn.

Many histological and cytological changes have been observed in patients treated with busulfan, including widespread dysplasia affecting uterine cervical, bronchial and other epithelia. Most reports relate to long-term treatment but transient epithelial abnormalities have been observed following short-term, high-dose treatment.

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/
Additionally, you can report to the company via the following address: Padagis.co.il

4.9 Overdose

Symptoms and signs

The acute dose-limiting toxicity of Busulfan in man is myelosuppression (see section 4.8*).*

The main effect of chronic overdose is bone marrow depression and pancytopenia.

Treatment

There is no known antidote to Busulfan. Haemodialysis should be considered in the management of overdose as there is one report of successful haemodialysis of Busulfan.

Appropriate supportive treatment should be given during the period of haematological toxicity.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Group and ATC code: Antineoplastic and Immunomodulating agents, alkyl sulfonates: *LO1 ABO1.*

Busulfan (1,4-butanediol dimethanesulfonate) is a bifunctional alkylating agent. Binding to DNA is believed to play a role in its mode of action and di-guanyl derivatives have been isolated but interstrand crosslinking has not been conclusively demonstrated.

The basis for the uniquely selective effect of busulfan on granulocytopoiesis is not fully understood. Although not curative, Busulfan is very effective in reducing the total granulocyte mass, relieving the symptoms of disease and improving the clinical state of the patient. Busulfan has been shown to be superior to splenic irradiation when judged by survival times and maintenance of haemoglobin levels and is as effective in controlling spleen size.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of oral Busulfan shows large intra-individual variations ranging from 47 % to 103 % (mean 80 %) in adults.

The area under the curve (AUC) and peak plasma concentrations (C_{max}) of Busulfan have been shown to be linearly dose dependent. Following administration of a single 2 mg oral dose of Busulfan, the AUC and C_{max} of Busulfan were 125 ± 17 nanograms.h/ml and 28 ± 5 nanograms/ml respectively.
A lag time between Busulfan administration and detection in the plasma of up to 2 h has been reported.

High-dose Treatment

Drug was assayed either using gas liquid chromatography with electron capture detection or by high-performance liquid chromatography (HPLC).

Following oral administration of high-dose Myleran (1 mg/kg every 6 h for 4 days), AUC and C_{max} in adults are highly variable but have been reported to be 8260 nanograms.h/ml (range 2484 to 21090) and 1047 nanograrns/ml (range 295 to 2558) respectively when measured by HPLC and 6135 nanograms.h/ml (range 3978 to 12304) and 1980 nanograms/ml (range 894 to 3800) respectively using gas chromatography.

Distribution

Busulfan is reported to have a volume of distribution of 0.64 ± 0.12 L/kg in adults.

Busulfan given in high-doses has recently been shown to enter the cerebrospinal fluid (CSF) in concentrations comparable to those found in plasma, with a mean CSF:plasma ratio of 1.3:1. The saliva:plasma distribution of Busulfan was 1.1:1.

The level of busulfan bound reversibly to plasma proteins has been variably reported to be insignificant or approximately 55 %. Irreversible binding of drug to blood cells and plasma proteins has been reported to be 47 % and 32 %, respectively.

Biotransformation
Busulfan metabolism involves a reaction with glutathione, which occurs via the liver and is mediated by glutathione-S-transferase.

The urinary metabolites of busulfan have been identified as 3-hydroxysulpholane, tetrahydrothiophene 1-oxide and sulpholane, in patients treated with high-dose Busulfan. Very little busulfan is excreted unchanged in the urine.

Elimination

Busulfan has a mean elimination half life of between 2.3 and 2.8 h. Adult patients have demonstrated a clearance of busulfan of 2.4 to 2.6 ml/min/kg. The elimination half life of busulfan has been reported to decrease upon repeat dosing suggesting that busulfan potentially increases its own metabolism.

Very little (1 to 2 %) busulfan is excreted unchanged in the urine.

Special patient populations

Paediatric population

The bioavailability of oral busulfan shows large intra-individual variation ranging from 22 % to 120 % (mean 68 %) in children.

Plasma clearance is reported to be 2 to 4 times higher in children than in adults when receiving 1 mg/kg every 6 h for 4 days. Dosing children according to body surface area has been shown to give AUC and C_{max} values similar to those seen in adults. The area under the curve has been shown to be half that of adults in children under the age of 15 years and a quarter of that of adults in children under 3 years of age.

Busulfan is reported to have a volume of distribution of 1.15 ± 0.52 L/kg in children.
When busulfan is administered at a dose of 1 mg/kg every 6 h for 4 days, the CSF:plasma ratio has been shown to be 1.02:1. However, when administered at a dose of 37.5 mg/m^2 every 6 h for 4 days the ratio was 1.39:1.

Obese Patients

Obesity has been reported to increase busulfan clearance. Dosing based on body surface area or adjusted ideal bodyweight should be considered in the obese.

5.3 Preclinical safety data

Busulfan has been shown to be mutagenic in various experimental systems, including bacteria, fungi, *Drosophila* and cultured mouse lymphoma cells.

In vivo cytogenetic studies in rodents have shown an increased incidence of chromosome aberrations in both germ cells and somatic cells after Busulfan treatment.

Carcinogenicity

There is limited evidence from preclinical studies that Busulfan is carcinogenic in animals (see section 4.4).

Teratogenicity

There is evidence from animal studies that busulfan produces foetal abnormalities and adverse effects on off-spring, including defects of the musculo-skeletal system, reduced body weight and size, impairment of gonad development and effects on fertility.

Fertility

Busulfan interferes with spermatogenesis in experimental animals. Limited studies in female animals indicate busulfan has a marked and irreversible effect on fertility through oocyte depletion.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:
Lactose, anhydrous
Pregelatinised starch
Magnesium stearate

Tablet coating:
Hypromellose
Titanium dioxide
Triacetin

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The expiry date of the product is indicated on the packaging materials.
After first opening use within 100 days.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Myleran 2 mg tablets are supplied in amber glass bottles with a child resistant closure containing 25 or 100 tablets.
Not all package sizes may be marketed.

6.6 Special precautions for disposal and other handling

Safe handling of Myleran tablets
The tablets should not be divided and provided the outer coating is intact, there is no risk in handling Myleran Tablets.
Handlers of Myleran Tablets should follow guidelines for the handling of cytotoxic drugs.

Disposal
Myleran tablets surplus to requirements should be destroyed in a manner appropriate for the destruction of dangerous substances.

7. Manufacturer

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

8. Registration Holder

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

9. Registration Number

129-38-30943-00

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