Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Myleran 2 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of the active substance busulfan.

Excipient with known effect:

Each tablet also contains 92.5mg of lactose.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, film-coated, biconvex tablets engraved 'GX EF3' on one side and 'M' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Myleran is indicated for the palliative treatment of the chronic phase of chronic myeloid leukaemia.

Myleran is effective in producing prolonged remission in polycythaemia vera, particularly in cases with marked thrombocytosis.

Myleran may be useful in selected cases of essential thrombocythaemia and myelofibrosis.

4.2 Posology and method of administration

Posology
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 patients
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.

Use in the elderly
No special comment.

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

Note: Lower doses of Myleran should be used if it is administered with other cytotoxic agents.

Paediatric population:
Chronic myeloid 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.

Polycythaemia vera:

The usual dose is 4 to 6 mg daily, continued for 4 to 6 weeks, with careful monitoring of the blood count, particularly the platelet count.

Further courses are given when relapse occurs; alternatively, maintenance therapy may be given using approximately half the induction dose.

If the polycythaemia is controlled primarily by venesection, short courses of Myleran may be given solely to control the platelet count.

Myelofibrosis:
The usual initial dose is 2 to 4 mg daily.

Very careful haematological control is required because of the extreme sensitivity of the bone marrow in this condition.

Essential thrombocythaemia
The usual dosage is 2 to 4 mg per day.

Treatment should be interrupted if the total leucocyte count falls below 5 x 10^9 per litre or the platelet count below 500 x 10^9 per litre.

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 reaction to busulfan or any other component of the preparation.

4.4 Special warnings and precautions for use

Myleran should only be administered under the direction of a specialist oncology service having the facilities for regular monitoring of clinical biochemical and haematological effects during and after administration.

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 used with care in patients with respiratory dysfunction. Pulmonary function should be monitored regularly in such individuals. 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 possible and careful attention given to post-operative respiratory care.

Hyperuricaemia and/or hyperuricosuria are not uncommon in patients with chronic myeloid 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.

Myleran has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolised 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, total 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).

High-dose Treatment (used for Haemopoietic Stem Cell Transplantation)

If high-dose Myleran is prescribed (see section 4.9), patients should be given prophylactic anticonvulsant therapy with preferably a benzodiazepine rather than phenytoin (see section 4.5 and 4.8).

Concomitant administration of itraconazole or metronidazole with high-dose busulfan has been reported to be associated with an increased risk of busulfan toxicity (see section 4.5). Co-administration of metronidazole and high-dose busulfan is not

recommended. Co-administration of itraconazole with high-dose busulfan should be at the discretion of the prescribing physician and should be based on a risk/benefit assessment.

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

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.

Bone marrow depression, particularly thrombocytopenia, occurs with busulfan therapy. Busulfan should be used only with extreme caution in patients whose bone marrow reserve may have been compromised by prior radiotherapy or treatment with other cytotoxic drugs. Administration should cease immediately in the event of a sharp fall in platelet count or the development of purpura. Daily dosage higher than 4 mg is associated with an increased risk of thrombocytopenia or irreversible marrow depression.

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).

Safe Handling of Myleran Tablets

See section 6.6.

Mutagenicity

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

Carcinogenicity

On the basis of short-term tests, Myleran has been classified as potentially carcinogenic by the IARC. 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.

Very careful consideration should be given to the use of Myleran for the treatment of polycythaemia vera and essential thrombocythaemia in view of the drug's carcinogenic potential (see section 5.3). The use of Myleran for these indications should be avoided in younger or asymptomatic patients. If the drug is considered necessary treatment courses should be kept as short as possible.

Oogenesis and spermatogenesis

Busulfan interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Men treated with busulfan should be informed about sperm preservation prior to treatment (section 4.6 and 4.8).

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 (see section 4.8).

In the paediatric population, for the combined Busulfan-Melphalan (BuMel) 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.

The administration of phenytoin to patients receiving high-dose Myleran (see section 4.9) may result in a decrease in the myeloablative 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 busulfan 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

Myleran can lead to suppression of ovarian function and amenorrhoea in women and suppression of spermatogenesis in men. It may cause sterility in both sexes. In women busulfan may cause severe and persistent ovarian failure, including failure to achieve puberty after administration to young girls and pre-adolescents at high-dose. It may also cause male infertility, azoospermia and testicular atrophy in male patients receiving busulfan (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 whenever possible during pregnancy, particularly during the first trimester. In every individual case the expected benefit of treatment to the mother must be weighed against the possible risks 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.

Studies of busulfan treatment in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is largely unknown.

Breast-feeding
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 busulfan 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 (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)
Blood and lymphatic system disorders	Very common	Dose-related bone marrow failure, manifesting as leukopenia and particularly thrombocytopenia
	Rare	Aplastic anaemia(see section 4.9)
Nervous system disorders	Rare	At high-dose: seizure (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 busulfan 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
	Not known	Pulmonary hypertension
Gastrointestinal disorders	Very common	At high-dose: nausea, vomiting, diarrhoea, mouth ulceration (see section 4.9)
	Rare	At conventional dose: nausea, vomiting, diarrhoea, mouth ulceration, which may possibly be ameliorated by usingdivided 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 hepatic necrosis
	Rare	Jaundice and hepatic function abnormal, at

System organ class	Frequency	Side effects
		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, porphyria non-acute, rash, dry skin and skin fragility with complete anhydrosis cheilosis.
Musculoskeletal and connective tissue disorders	Rare	Sjögren's syndrome
Injury, poisoning and procedural complications	Rare	Radiation skin injury is increased in patients receiving radiotherapy soon after high-dose busulfan
Renal and urinary disorders	Common	At high-dose: cyctitis haemorrhagic in combination with cyclophosphamide
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 pubertal failure after administration to young girls and pre-adolescents at high-dose. Male infertility, azoospermia and testicular atrophy in male patients receiving busulfan
	Uncommon	Ovarian disorder and amenorrhoea with menopausal symptoms in pre-menopausal patients at conventional dose.
	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 busulfan.

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. It is possible that subsequent radiotherapy can augment subclinical lung injury caused by busulfan. Other cytotoxic agents may cause additive lung toxicity. (see section 4.5). 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 busulfan 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 myeloid leukaemia showed evidence of centrilobular sinusoidal fibrosis.

The combination of busulfan and thioguanine is associated with significant hepatotoxicity (see section 4.5).

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).

In very rare cases, recovery of ovarian function has been reported with continuing treatment.

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 busulfan 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 (see section 4.9).

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. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms and signs:
The acute dose-limiting toxicity of Myleran in man is myelosuppression (see Section 4.8 *Undesirable Effects*).

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

If high-dose Myleran is used in association with bone marrow transplantation (The usual total dose of Myleran, given in combination with other agents is 14 to 16 mg/kg given orally over 4 consecutive days (3.5 to 4 mg/kg/day in divided doses)), gastro-intestinal toxicity becomes dose-limiting, with mucositis, nausea, vomiting, diarrhoea and anorexia.

Treatment:
There is no known antidote. Dialysis should be considered in the management of overdose as there is one report of successful dialysis of busulfan.

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

Since, busulfan is metabolised through conjugation with glutathione, administration of glutathione might be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Group and ATC code: Antineoplastic and Immunomodulating agents, alkyl sulfonates: L01AB01.

Mechanism of action
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, Myleran is very effective in reducing the total granulocyte mass, relieving the symptoms of disease and improving the clinical state of the patient. Myleran 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 intraindividual variation ranging from 47 % to 103 % (mean 80 %) in adults.

The area under the curve (AUC) and peak plasma concentrations (Cmax) of busulfan have been shown to be linearly dose dependent. Following administration of a single 2 mg oral dose of busulfan, the AUC and Cmax of busulfan were125 ± 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 busulfan (1 mg/kg every 6 h for 4 days), AUC and Cmax in adults are highly variable but have been reported to be 8260 nanograms.h/ml (range 2484 to 21090) and 1047 nanograms/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 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-Stransferase.

The urinary metabolites of busulfan have been identified as 3-hydroxysulpholane, tetrahydrothiophene 1-oxide and sulpholane, in patients treated with high-dose busulfan.

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 – 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 Cmax 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/m2 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

Mutagenicity

Busulfan has been shown to be mutagenic in various experimental systems, including bacteria (Ames Salmonella test), 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 insufficient evidence from preclinical studies to determine whether busulfan has carcinogenic potential (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 gonadal 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 via oocyte depletion.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Anhydrous lactose
Pregelatinised starch
Magnesium stearate

Tablet coating:
Hypromellose
Titanium dioxide
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 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 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Safe handling of Myleran tablets:
Provided the outer coating is intact, there is no risk in handling Myleran tablets.The tablets should not be divided.

Handlers of Myleran tablets should follow guidelines for the handling of cytotoxic drugs according to local requirements and/or regulations (i.e. Royal Pharmaceutical Society of Great Britain Working Party on the Handling of Cytotoxic Drugs).

Pregnant staff should not handle cytotoxic agents.

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

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 April 1979
Date of last renewal: 1 April 2009

10 DATE OF REVISION OF THE TEXT

June 2025