Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Melphalan Teva 50 mg Powder and solvent for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg melphalan (as melphalan hydrochloride).

After reconstitution 1 ml of solution contains 5 mg melphalan.

Excipients with known effect
Each vial of solvent contains 53.5 mg sodium, 402 mg ethanol anhydrous and 6.220 g propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.

Powder: White or almost white freeze-dried powder.
Solvent: Clear, colourless solution.

The pH of the reconstituted solution is approximately 6.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Melphalan Teva, at conventional intravenous dosage, is indicated in the treatment of multiple myeloma and ovarian cancer.

Melphalan Teva, at high intravenous dosage, is indicated, with or without haematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma.

Melphalan Teva, administered by regional arterial perfusion, is indicated in the treatment of localised malignant melanoma of the extremities and localised soft tissue sarcoma of the extremities.

In the above indications, Melphalan Teva may be used alone or in combination with other cytotoxic drugs.

4.2 Posology and method of administration

Posology

Parenteral administration
Melphalan Teva is for intravenous use and regional arterial perfusion only.
Melphalan Teva should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m^2.

Multiple myeloma: Melphalan Teva is administered on an intermittent basis alone, or in combination with other cytotoxic drugs. Administration of prednisone has also been included in a number of regimens.

When used as a single agent, a typical intravenous Melphalan Teva dosage schedule is 0.4 mg/kg body weight (16 mg/m^2 body surface area) repeated at appropriate intervals (e.g. once every 4 weeks), provided there has been

recovery of the peripheral blood count during this period.

High-dose regimens generally employ single intravenous doses of between 100 and 200 mg/m^2 body surface area (approximately 2.5 to 5.0 mg/kg body weight), but haematopoietic stem cell rescue becomes essential following doses in excess of 140 mg/m^2 body surface area. Hydration and forced diuresis are also recommended.

Ovarian adenocarcinoma: When used intravenously as a single agent, a dose of 1 mg/kg body weight (approximately 40 mg/m^2 body surface area) given at intervals of 4 weeks has often been used.

When combined with other cytotoxic drugs, intravenous doses of between 0.3 and 0.4 mg/kg body weight (12 to 16 mg/m^2 body surface area) have been used at intervals of 4 to 6 weeks.

Advanced neuroblastoma: Doses of between 100 and 240 mg/m^2 body surface area (sometimes divided equally over 3 consecutive days) together with haematopoietic stem cell rescue, have been used either alone or in combination with radiotherapy and/or other cytotoxic drugs.

Malignant melanoma: Hyperthermic regional perfusion with melphalan has been used as an adjuvant to surgery for early malignant melanoma and as palliative treatment for advanced but localised disease. The scientific literature should be consulted for details of perfusion technique and dosage used. A typical dose range for upper extremity perfusions is 0.6−1.0 mg/kg bodyweight and for lower extremity perfusions is 0.8−1.5 mg/kg body weight.

Soft tissue sarcoma: Hyperthermic regional perfusion with melphalan has been used in the management of all stages of localised soft tissue sarcoma, usually in combination with surgery. A typical dose range for upper extremity perfusions is 0.6−1.0 mg/kg body weight and for lower extremity perfusions is 1−1.4 mg/kg body weight.

Paediatric population
Melphalan at conventional dosage, is only rarely indicated in children and dosage guidelines cannot be stated.

High dose melphalan injection, in association with haematopoietic stem cell rescue, has been used in childhood neuroblastoma and dosage guidelines based on body surface area, as for adults, may be used.

Elderly
Although melphalan is frequently used at conventional dosage in the elderly, there is no specific information available relating to its administration to this patient sub-group.

Experience in the use of high dose melphalan in elderly patients is limited. Consideration should therefore be given to ensure adequate performance status and organ function, before using high dose Melphalan Tevain elderly patients.

Renal impairment
Melphalan clearance, though variable, may be decreased in renal impairment.

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

When Melphalan Teva is used at conventional intravenous dosage (16−40 mg/m^2 body surface area), it is recommended that the initial dose should be reduced by 50% and subsequent dosage determined according to the degree of haematological suppression.

For high intravenous doses of melphalan (100 to 240 mg/m^2 body surface area), the need for dose reduction depends upon the degree of renal impairment, whether haematopoietic stem cells are re-infused, and therapeutic need. Melphalan Teva should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m^2.

As a guide, for high dose melphalan treatment without haematopoietic stem cell rescue in patients with moderate renal

impairment (creatinine clearance 30 to 50 ml/min) a dose reduction of 50% is usual. High dose melphalan (above 140 mg/m^2) without haematopoietic stem cell rescue should not be used in patients with more severe renal impairment.

High dose melphalan with haematopoietic stem cell rescue has been used successfully even in dialysis dependent patients with end-stage renal failure. The relevant literature should be consulted for details.

Method of administration

For intravenous administration, it is recommended that Melphalan Teva solution is injected slowly into a fast-running infusion solution via a swabbed injection port.

If direct injection into a fast-running infusion is not appropriate, Melphalan Teva solution may be administered diluted in an infusion bag.

Melphalan Teva is not compatible with infusion solutions containing dextrose and it is recommended that only sodium chloride intravenous infusion 0.9% w/v is used. For instructions on dilution before administration, see section 6.6.

When further diluted in an infusion solution, Melphalan Teva has reduced stability and the rate of degradation increases rapidly with rise in temperature. If Melphalan Teva is infused at a room temperature of approximately 25°C, the total time from preparation of the injection solution to the completion of infusion should not exceed 1.5 hours.

Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions, the preparation must be discarded.

Care should be taken to avoid possible extravasation of Melphalan Teva and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.

If high dose Melphalan Teva is administered with or without autologous bone marrow transplantation, administration via a central venous line is recommended.

For regional arterial perfusion, the literature should be consulted for detailed methodology.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Melphalan Teva is a cytotoxic drug, which falls into the general class of alkylating agents. It should be prescribed only by physicians experienced in the management of malignant disease with such agents. As with all high dose chemotherapy, precautions should be taken to prevent tumour lysis syndrome.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Since melphalan is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary.

Melphalan solution can cause local tissue damage, should extravasation occur and consequently, it should not be administered by direct injection into a peripheral vein. It is recommended that Melphalan Teva solution is administered by injecting slowly into a fast-running intravenous infusion via a swabbed injection port, or via a central venous line.

In view of the hazards involved and the level of supportive care required, the administration of high dose melphalan should be confined to specialist centres, with the appropriate facilities and only be conducted by experienced clinicians.

In patients receiving high dose melphalan, consideration should be given to the prophylactic administration of anti-

infective agents and the administration of blood products as required.

Consideration should be given to ensure adequate performance status and organ function before using high dose melphalan. melphalan should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m^2.

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

Safe handling of Melphalan Teva
The handling of Melphalan Teva formulations should follow guidelines for the handling of cytotoxic drugs.

Monitoring
Since melphalan is a potent myelosuppressive 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 leukocyte or platelet counts, treatment should be temporarily interrupted. Melphalan Teva should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

Renal impairment
Melphalan clearance may be reduced in patients with renal impairment who may also have uraemic marrow suppression. Dose reduction may therefore be necessary (see section 4.2). See section 4.8 for elevation of blood urea.

Mutagenicity
Melphalan is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the drug.

Carcinogenicity
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, multiple myeloma, 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.

Effects on fertility
Melphalan 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 melphalan can have an adverse effect on spermatogenesis. Therefore, it is possible that melphalan may cause temporary or permanent sterility in male patients.

Melphalan Teva contains ethanol, sodium and propylene glycol.
This medicinal product contains 5.1 vol % ethanol, i.e. up to 2894 mg per dose, equivalent to 73.4 ml beer or 30.6 ml wine.
Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breast-feeding women, in children and high-risk groups such as patients with liver disease, or epilepsy.

This medicinal product contains 53.5 mg sodium per vial, equivalent to 2.7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains 6.220 g propylene glycol per vial which is equivalent to 760 mg/kg/dose, based on the

maximum recommended dose of the medicinal product (calculated for BSA=1.8 m^2 and 70 kg).
Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol.
Therefore doses higher than 500 mg/kg/day may be administered in children > 5 years old but will have to be considered case by case.
Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis.
Medical monitoring is required.

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).

Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic entercolitis.

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

4.6 Fertility, pregnancy and lactation

Contraception for men and women of childbearing potential
As with all cytotoxic treatments, male and female patients who use Melphalan Teva
should use the effective and reliable contraceptive methods up until three months after cessation of treatment.

Pregnancy
There are no or limited amount of data from the use of melphalan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Risk for human is not known, but due to the mutagenic properties and structural similarity of melphalan with known teratogenic compounds, it is possible that melphalan can induce congenital malformations in offspring of treated patients. Melphalan should not be used during pregnancy unless the clinical condition of the woman requires treatment with melphalan.

Breastfeeding
It is unknown whether melphalan or its metabolites are excreted in human milk.
Mothers receiving Melphalan Teva should not breastfeed.

Fertility
Melphalan causes suppression of ovary function in premenopausal women, resulting in amenorrhea in a large number of patients. There is evidence from some animal studies that melphalan can have an adverse effect on spermatogenesis (see section 5.3). Therefore it is possible that melphalan may cause temporary or permanent sterility in male patients. It is recommended that men who are receiving treatment with melphalan do not father a child during treatment and up to 6 months afterwards and that they have 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

Not relevant.

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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), 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 (see Skin and subcutaneous tissue disorders)

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

The incidence of diarrhoea, 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 gastro-intestinal damage induced by high-dose melphalan and the literature should be consulted for details.

Hepatobiliary disorders
Rare: hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice; veno occlusive disease following high dose treatment

Skin and subcutaneous tissue disorders
Very common: alopecia at high dose
Common: alopecia at conventional dose
Rare: maculopapular rashes and pruritus (see Immune system disorders)

Musculoskeletal and connective tissue disorders
Injection, following isolated limb perfusion:

Very common: muscle atrophy, muscle fibrosis, myalgia, blood creatine phosphokinase increased
Common: compartment syndrome
Not known: muscle necrosis, rhabdomyolysis

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.

General disorders and administration site conditions
Very common: subjective and transient sensation of warmth and/or tingling

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 the HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Gastro-intestinal effects, including nausea, vomiting and diarrhoea are the most likely signs of acute oral overdosage. The immediate effects of acute intravenous overdosage are nausea and vomiting. Damage to the gastro-intestinal mucosa may also ensue and diarrhoea, sometimes haemorrhagic, has been reported after overdosage. The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia.

General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary and consideration given to hospitalisation, antibiotic cover, 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 agents, alkylating agents, nitrogen mustard analogues, ATC code: L01AA03

Melphalan is a bifunctional alkylating agent. 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, crosslinking the 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.

Distribution
Melphalan is moderately bound to plasma proteins with reported percent binding ranging from 69% to 78%. There is evidence that the protein binding is linear in the range of plasma concentrations usually achieved in standard dose therapy, but that the binding may become concentration-dependent at the concentrations observed in high-dose therapy. Serum albumin is the major binding protein, accounting for about 55 to 60% the binding, and 20% is bound to α_1-acid glycoprotein. In addition, melphalan binding studies have revealed the existence of an irreversible component attributable to the alkylation reaction with plasma proteins.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m^2 body surface area (approximately 0.1 to 0.6 mg/kg bodyweight) to 10 patients with ovarian cancer or multiple myeloma, the mean volumes of distribution at steady state and central compartment were 29.1 ± 13.6 litres and 12.2 ± 6.5 litres, respectively.

In 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2- to 20−min infusion, the mean volumes of distribution at steady state and central compartment were, respectively, 40.2 ± 18.3 litres and 18.2 ± 11.7 litres.

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.

Biotransformation
In vivo and *in vitro* data suggest that spontaneous degradation rather than enzymatic metabolism is the major determinant of the drug's half-life in man.

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 8 patients given a single bolus dose of 0.5 to 0.6 mg/kg bodyweight, the composite initial and terminal half-lives were reported to be 7.7 ± 3.3 min and 108 ± 20.8 min, respectively. Following injection of melphalan, monohydroxymelphalan and dihydroxymelphalan were detected in the patients' plasma, reaching peak levels at approximately 60 min and 105 min, respectively. A similar half-life of 126 ± 6 min was seen when melphalan was added to the patients' serum *in vitro* (37°C), suggesting that spontaneous degradation rather than enzymic metabolism may be the major determinant of the drug's half-life in man.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m^2 body surface area (approximately 0.1 to 0.6 mg/kg bodyweight) to 10 patients with ovarian cancer or multiple myeloma, the pooled initial and terminal half-lives were, respectively, 8.1 ± 6.6 min and 76.9 ± 40.7 min. A mean clearance of 342.7 ± 96.8 ml/min was recorded.

In 15 children and 11 adults given high-dose i.v. melphalan (140 mg/m^2 body surface area) with forced diuresis, the mean initial and terminal half-lives were found to be 6.5 ± 3.6 min and 41.4 ± 16.5 min, respectively. Mean initial and terminal half-lives of 8.8 ± 6.6 min and 73.1 ± 45.9 min, respectively, were recorded in 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2- to 20−min infusion. The mean clearance was 564.6 ± 159.1 ml/min.

Following hyperthermic (39°C) perfusion of the lower limb with 1.75 mg/kg bodyweight, mean initial and terminal half-lives of 3.6 ± 1.5 min and 46.5 ± 17.2 min, respectively, were recorded in 11 patients with advanced malignant melanoma. A mean clearance of 55.0 ± 9.4 ml/min was recorded.

Special patient populations

Renal impairment
Melphalan clearance may be decreased in renal impairment (see sections 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 a cytostatic agent and mutagenicity has therefore not been thoroughly investigated in pre-clinical studies. Melphalan was mutagenic in vivo causing chromosomal aberrations. Clinical information on potential toxicity of melphalan is provided in sections 4.4 and 4.6.

Reproductive toxicity and fertility
Melphalan was teratogenic in rat after single dose exposure in reproductive toxicity studies. In repeated dose reproductive toxicity studies, melphalan was maternal toxic and induced congenital malformations, intra-uterine death, growth retardation and disrupted development.

A single dose of melphalan in male mice induced cytotoxicity and chromosomal aberrations in sperm cells. In female mice a reduction in number of pups per litter was observed. After recovery the number of pups per litter was also reduced over time, which was related to a reduced number of follicles.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Povidone K12
Hydrochloric acid (for pH-adjustment)

Solvent:
Sodium citrate
Propylene glycol
Ethanol anhydrous
Water for Injections

6.2 Incompatibilities

Melphalan is not compatible with infusion solutions containing dextrose.

6.3 Shelf life

The shelf life for the medicinal product as packed for sale (unopened product):
18 months.

Shelf life after reconstitution:
Chemical and physical in-use stability is limited and the solution should be prepared immediately before use. The reconstituted solution (5 mg/ml) should be transferred into the infusion bag in less than 30 minutes and the diluted solution should be completely administered within 1 hour of reconstitution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder:
Type I colourless glass vial (15 ml), closed with type I bromobutyl rubber stopper and aluminium metal cap with polypropylene disk. The vial may be or may not be sheathed in a protective sleeve.

Solvent:
Type I colourless glass vial (10 ml), closed with type I bromobutyl rubber stopper and aluminium metal cap with polypropylene disk.

Pack size: single pack containing 1 vial of powder and 1 vial of solvent.

6.6 Special precautions for disposal and other handling

Precautions
MELPHALAN TEVA IS AN ACTIVE CYTOTOXIC AGENT FOR USE UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS. Caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

Safe handling of Melphalan Teva

The handling of Melphalan Tevaformulations should follow guidelines for the handling of cytotoxic drugs.

Preparation of Melphalan Teva powder and solvent for solution for injection/infusion
Melphalan Teva solution for injection/infusion should be prepared at room temperature (approximately 25°C), by reconstituting the freeze-dried powder with the solvent provided.
It is important that both the freeze-dried powder and the solvent provided are at room temperature before starting reconstitution. Warming the diluent in the hand may aid reconstitution. 10 ml of this vehicle should be added quickly, as a single quantity into the vial containing the freeze dried powder, and immediately shaken vigorously (for approximately 1 minute) until a clear solution, without visible particles, is obtained. Each vial must be reconstituted individually in this manner. The resulting solution contains the equivalent of 5 mg/ml melphalan.

Melphalan Teva solution has limited stability and should be prepared immediately before use. Any solution unused after one hour should be discarded according to standard guidelines for handling and disposal of cytotoxic drugs.

The reconstituted solution is clear, colourless to slightly yellowish solution free of visible particles, with a final pH of approximately 6.5.

If visible turbidity or crystallization occurs in the diluted solution for infusion, this solution should be discarded.

The reconstituted solution should not be refrigerated as this will cause precipitation.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/077/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th May 2018

10 DATE OF REVISION OF THE TEXT