Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cytarabine Teva 100 mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 100 mg cytarabine.

Each 1 ml vial contains 100 mg cytarabine.
Each 5 ml vial contains 500 mg cytarabine.
Each 10 ml vial contains 1000 mg cytarabine.
Each 20 ml vial contains 2000 mg cytarabine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

The product is a clear, colourless to pale yellow solution.
pH: 7.0 – 9.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For induction of remission in acute myeloid leukaemia in adults and for other acute leukaemias of adults and children.

4.2 Posology and method of administration

Posology

Treatment with cytarabine should be initiated by, or be in consultation with, a doctor with extensive experience in treatment with cytostatics. Only general recommendations can be given, as acute leukaemia is almost exclusively treated with combinations of cytostatics.

Dosage recommendations may be made according to body weight (mg/kg) or according to BSA (mg/m^2). Dosage recommendations may be converted from those in terms of bodyweight to those related to surface area by means of nomograms.

1. Remission induction

Induction therapy dosage and schedule vary depending on the regimen used.

a) Continuous treatment

The following dose regimens have been used for continuous treatment in remission induction.

i) Rapid injection - 2 mg/kg/day is a judicious starting dose. Administer for 10 days. Obtain daily blood counts. If no antileukaemic effect is noted and there is no apparent toxicity, increase to 4 mg/kg/day and maintain until therapeutic response or toxicity is evident. Almost all patients can be carried to toxicity with these doses.

ii) 0.5 - 1.0 mg/kg/day may be given in an infusion of up to 24 hours duration. Results from one hour infusions have been satisfactory in the majority of patients. After 10 days this initial daily dose may be increased to 2 mg/kg/day subject to toxicity. Continue to toxicity or until remission occurs.

b) Intermittent treatment

The following dose regimens have been used for intermittent treatment in remission induction.

i) 3-5 mg/kg/day is administered intravenously on each of five consecutive days. After a two to nine day rest period, a further course is given. Continue until response or toxicity occurs.

The first evidence of marrow improvement has been reported to occur 7–64 days (mean 28 days) after the beginning of therapy.

In general, if a patient shows neither toxicity nor remission after a fair trial, the cautious administration of higher doses is warranted. As a rule, patients have been seen to tolerate higher doses when given by rapid intravenous injection as compared with slow infusion. This difference is due to the rapid metabolism of cytarabine and the consequent short duration of action of the high dose.

ii) Cytarabine 100-200 mg/m^2/24 hours, as continuous infusion for 5–7 days alone or in combination with other cytostatics including for instance an anthracycline, has been used. Additional cycles may be administered at intervals of 2–4 weeks, until remission is achieved or unacceptable toxicity occurs.

2. Maintenance therapy

Maintenance dosage and schedule vary depending on the regimen used.

The following dose regimens have been used for continuous treatment following remission induction.

i) Remissions, which have been induced by cytarabine, or by other drugs, may be maintained by intravenous or subcutaneous injection of 1 mg/kg once or twice weekly.

ii) Cytarabine has also been administered in doses of 100-200 mg/m^2, as continuous infusion for 5 days at monthly intervals as monotherapy or in combination with other cytostatics.

High dosage
Cytarabine, under strict medical surveillance, is administered as monotherapy or in combination with other cytostatics, at a dose of **2-3 g/m^2** via intravenous infusion over 1-3 hours every 12 hours for 2−6 days (total of 12 doses per cycle). A total treatment dose of 36 g/m^2 should not be exceeded. Frequency of treatment cycles depends on the response to treatment and haematological and non-haematological toxicity. Also refer to precautions (see section 4.4) for treatment stopping requirements.

Paediatric population
Safety in infants has not been established.

Hepatic and renal impairment
Patients with impaired hepatic or renal function: Dosage should be reduced.

Cytarabine can be dialyzed. Therefore, cytarabine should not be administered immediately before or after a dialysis.

Elderly patients
High dose therapy in patients >60 years should be administered only after careful risk benefit evaluation.

Method of administration

For instructions on dilution of the medicinal product before administration, see section 6.6.

Cytarabin 100 mg/ml solution is intended for intravenous infusion or injection, or subcutaneous injection.

Subcutaneous injection is generally well tolerated, and may be recommended when used in maintenance therapy.

Cytarabine 100 mg/ml should not be administered by the intrathecal route.

4.3 Contraindications

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

Anaemia, leucopenia and thrombocytopenia of non-malignant aetiology (e.g. bone marrow aplasia); unless the clinician feels that such management offers the most hopeful alternative for the patient.

Degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionizing radiation.

4.4 Special warnings and precautions for use

Paediatric population
The safety of this drug for use in infants is not established.

Warnings
Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leucocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood.

Facilities should be available for management of complications, possibly fatal, of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defences, and haemorrhage secondary to thrombocytopenia).

Anaphylactic reactions have occurred with cytarabine treatment. One case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following some experimental cytarabine dose schedules. These reactions include: reversible corneal toxicity; cerebral and cerebellar dysfunction (usually reversible); somnolence; convulsion; severe gastro-intestinal ulceration, including pneumatosis cystoides intestinalis, leading to peritonitis; sepsis; liver abscess; and pulmonary oedema.

Cytarabine has been shown to be carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

Precautions
Patients receiving cytarabine must be monitored closely. Frequent platelet and leucocyte counts are mandatory. Suspend or modify therapy when drug induced marrow depression has resulted in a platelet count under 50,000 or a polymorphonuclear count under 1,000 per cubic mm. Counts of formed elements in the peripheral blood may continue to fall after the drug is stopped, and reach lowest values after drug free intervals of five to seven days. If indicated, restart therapy when definite signs of marrow recovery appear (on successive bone marrow studies). Patients whose drug is withheld until 'normal' peripheral blood values are attained may escape from control.

Peripheral motor and sensory neuropathies after consolidation with high doses of cytarabine, daunorubicin, and asparaginase have occurred in adult patients with acute non lymphocytic leukaemia. Patients treated with high doses of

cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary oedema have occurred following high dose schedules with cytarabine therapy.

When intravenous doses are given quickly, patients are frequently nauseated and may vomit for several hours afterwards. This problem tends to be less severe when the drug is infused.

Abdominal tenderness (peritonitis) and guaiac positive colitis, with concurrent neutropenia and thrombocytopenia, have been reported in patients treated with conventional doses of cytarabine in combination with other drugs. Patients have responded to non-operative medical management.

Delayed progressive ascending paralysis resulting in death has been reported in children with AML following intravenous cytarabine at conventional doses in combination with other drugs.

Both hepatic and renal function should be monitored during cytarabine therapy. In patients with pre-existing liver impairment cytarabine should be administered only with utmost care.

Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving cytarabine.

Like other cytotoxic drugs, cytarabine may induce hyperuricaemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacological measures as may be necessary to control this problem.

Vaccine/Immunosuppressant Effects/Increased Susceptibility to Infections
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cytarabine may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cytarabine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

High-dose
The risk of CNS side effects is higher in patients who have previously had CNS treatment as intrathecal chemotherapy or radiation therapy.

Concurrent granulocyte transfusion should be avoided, as severe respiratory insufficiency has been reported.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.

4.5 Interaction with other medicinal products and other forms of interaction

5-Fluorocytosine
5-Fluorocytosine should not be administered with cytarabine as the therapeutic efficacy of 5−fluorocytosine has been shown to be abolished during such therapy.

Digoxin
Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine or procarbazine. Steady-state plasma digitoxin concentrations did not appear to change. Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilisation of digitoxin for such patients may be considered as an alternative.

Gentamicin
An *in vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. In patients on cytarabine being treated with gentamicin for a *K.pneumoniae*

infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

Use of cytarabine alone or in combination with other immunosuppressive agents
Due to immunosuppressive action of cytarabine injection, viral, bacterial, fungal, parasitic, or saprophytic infections (in any location in the body) may be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

4.6 Fertility, pregnancy and lactation

Pregnancy
Cytarabine is known to be teratogenic in some animal species. The use of cytarabine in women who are or may become pregnant should be undertaken only after due consideration of the potential benefits and hazards.

Women have to use effective contraception during and up to 6 months after treatment.

Breast-feeding
This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding.

Fertility
Fertility studies to assess the reproductive toxicity of cytarabine have not been conducted. Gonadal suppression, resulting in amenorrhoea or azoospermia, may occur in patients taking cytarabine therapy, especially in combination with the alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible (see section 4.8). Given that cytarabine has a mutagenic potential which could induce chromosomal damage in the human spermatozoa, males undergoing cytarabine treatment and their partner should be advised to use a reliable contraceptive method during and up to 6 months after treatment.

4.7 Effects on ability to drive and use machines

Cytarabine has no influence on the ability to drive and use machines. Nevertheless, patients receiving chemotherapy may have an impaired ability to drive or operate machinery and should be warned of this possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects

The following adverse events have been reported in association with cytarabine therapy:

Frequencies are defined using the following convention:
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)
Not known (cannot be estimated from the available data)

Undesirable effects from cytarabine are dose-dependent. Most common are gastro-intestinal undesirable effects. Cytarabine is toxic to the bone marrow, and causes haematological undesirable effects.

Infections and infestations
Uncommon: Sepsis (immunosuppression), cellulitis at injection site.

Neoplasm benign, malignant and unspecified (Incl. cysts and polyps)
Uncommon: Lentigo.

Blood and lymphatic system disorders
Common: Anaemia, megaloblastosis, leucopenia, thrombocytopenia.

Not Known: Reduced reticulocytes.

The severity of these reactions is dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Immune system disorders
Uncommon: Anaphylaxis.
Not known: Allergic oedema.

Metabolism and nutrition disorders
Common: Anorexia, hyperuricaemia.

Nervous system disorders
Common: At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus.
Uncommon: Headache, peripheral neuropathy.
Not known: Neural toxicity, neuritis, dizziness.

Eye disorders
Common: Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis. These phenomena can be prevented or decreased by installation of corticosteroid eye drops.
Not known: Conjunctivitis (may occur with rash).

Cardiac disorders
Uncommon: Pericarditis.
Very rare: Arrhythmia.

Respiratory, thoracic and mediastinal disorders
Uncommon: Pneumonia, dyspnoea, sore throat.

Gastrointestinal disorders
Common: Dysphagia, abdominal pain, nausea, vomiting, diarrhoea, oral / anal inflammation or ulceration.
Uncommon: Esophagitis, oesophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis, peritonitis.
Not known: Pancreatitis.

Hepatobiliary disorders
Common: Reversible effects on the liver with increased enzyme levels.
Uncommon: Jaundice.
Not known: Hepatic dysfunction, liver abscess.

Skin and subcutaneous tissue disorders
Common: Reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia.
Uncommon: Skin ulceration, pruritus**,** burning pain of palms and soles.
Very rare: Neutrophilic eccrine hidradenitis.
Not known: Freckling, rash.

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia, arthralgia.

Renal and urinary disorders
Common: Renal impairment, urinary retention.

General disorders and administration site conditions
Common: Fever, thrombophlebitis at the injection site.
Uncommon: Chest pain.

Cytarabine (Ara-C) Syndrome (Immunoallergic effect):
A cytarabine syndrome has been descriped. It is characterised by fever, myalgia, bone pain, occasional chest pain, exanthema, conjuctivitis and nausea. It usually occurs 6−12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are serious enough to warrant treatment, corticosteroids should be contemplated as well as continuation of therapy with cytarabine.

Adverse effects due to high dose cytarabine treatment, other than those seen with conventional doses include:

Blood and lymphatic system disorders
Haematological toxicity, which manifests as profound pancytopenia, which may last 15-25 days along with more severe bone marrow aplasia than that observed at conventional doses.

Nervous system disorders
After treatment with high doses of cytarabine, symptoms of cerebral or cerebellar influence, such as personality changes, affected alertness, dysarthria, ataxia, tremor, nystagmus, headache, confusion, somnolence, dizziness, coma, convulsions, etc., appear in 8-37 % of treated patients. Peripheral motor and sensory neuropathies have also been reported with high dose therapy. The incidence in elderly people (>55 years) may be even higher. Other predisposing factors are impaired liver and renal function, previous CNS treatment (e.g. radiotherapy) and alcohol abuse. CNS disturbances are in most cases reversible.

The risk of CNS toxicity increases if the cytarabine treatment is given as high dose i.v. and combined with another CNS toxic treatment such as radiation therapy or high dose of a cytotoxic agent.

Eye disorders
Corneal and conjunctival toxicity: Reversible lesions of corneal and haemorrhagic conjunctivitis have been described. These phenomena can be prevented or decreased by installation of corticosteroid eye drops.

Skin and subcutaneous tissue disorders
Skin rash leading to desquamation, alopecia.

Infections and infestations
Viral, bacterial, fungal, parasitic or saprophytic infections in any location in the body may be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild but can be severe.

Gastrointestinal disorders
Especially during treatment with high doses of cytarabine, more severe reactions may appear in addition to common symptoms. Intestinal perforation or necrosis with ileus and peritonitis have been reported.

Hepatobiliary disorders
Liver abscesses, hepatomegaly, Budd-Chiari-syndrome (hepatic venous thrombosis) and pancreatitis have been observed after high-dose therapy.

Respiratory, thoracic and mediastinal disorders
Clinical signs as present in pulmonary oedema/ARDS may develop, particularly in high-dose therapy. The reaction is probably caused by an alveolar capillary injury. It is difficult to make an assessment of frequencies (stated as 10-26 % in different publications), since the patients usually have been in relapse where other factors may contribute to this reaction.

Others:
Following cytarabine therapy, cardiomyopathy and rhabdomyolysis have been reported. One case of anaphylaxis that resulted in cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

The gastro-intestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoids are recommended as prophylaxis of haemorrhagic conjunctivitis.

Amenorrhoea and azoospermia (see section 4.6).

Cytarabine is not recommended for intrathecal use; however, the following side effects have been reported with such use. Expected systemic reactions: bone marrow depression, nausea, vomiting. Occasionally, severe spinal cord toxicity even leading to quadriplegia and paralysis, necrotising encephalopathy, blindness and other isolated neurotoxicities have been reported.

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, 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

No specific antidote. Management advised following overdose is as follows: Cessation of therapy, followed by management of subsequent bone marrow depression, including whole blood or platelet transfusion and antibiotics as required. Twelve doses of 4.5 g/m^2 by IV infusion over one hour every 12 hours induces irreversible and fatal central nervous system toxicity.

Cytarabine may be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogues, ATC code: L01BC01

Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent, which inhibits the synthesis of deoxyribonucleic acid specifically in the S phase of the cell cycle. It also has antiviral and immunosuppressant properties. Detailed studies on the mechanism of cytotoxicity *in vitro* suggests that the primary action of cytarabine is inhibition of deoxycytidine synthesis via its active triphosphate metabolite arabinofuranosyl cytosine triphosphate ARA-CTP, although inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions.

High dose cytarabine regimens can overcome the resistance of leukemic cells no longer responding to conventional doses. Several mechanisms appear to be involved to this resistance:

- Increases in the quantity of substrate
- Increase in the intracellular pool of ARA-CTP, since there is a positive correlation between intracellular retention of ARA-CTP and percentage of cells in S-phase.

5.2 Pharmacokinetic properties

Cytarabine is deaminated to arabinofuranosyl uracil in the liver and kidneys. After intravenous administration to humans, only 5.8% of the administered dose is excreted unaltered in urine within 12-24 hours, 90% of the dose is excreted as the inactive deaminated product, arabinofuranosyl uracil (ARA-U). Cytarabine appears to be metabolised rapidly, primarily by the liver and perhaps by the kidney. After single high intravenous doses, blood levels fall to unmeasurable levels within 15 minutes in most patients. Some patients have indemonstrable circulating drug as early as 5 minutes after injection. The half-life of the drug is 10 minutes.

High dose cytarabine achieves plasma peak levels 200 fold higher than that observed with conventional dose regimens. The peak of inactive metabolite ARA-U, with high dose regimen, is observed after only 15 minutes. The renal clearance is slower with high dose cytarabine than with conventional dose cytarabine. The cerebrospinal fluid (CSF)

levels achieved, after high dose (1−3 g/m^2) cytarabine via intravenous infusion, are around 100-300 nanograms/ml.

Peak plasma levels are achieved about 20-60 minutes after subcutaneous application. At comparable doses, they are significantly lower than plasma levels achieved after intravenous administration.

5.3 Preclinical safety data

Cytarabine is embryotoxic and teratogenic when administered to rodents during the period of organogenesis at clinically relevant doses. It is reported that cytarabine causes developmental toxicity, including damage to the developing brain, when administered during the peri- and postnatal period. No formal fertility studies have been reported however sperm head abnormalities were observed following cytarabine treatment in mice.
Cytarabine is mutagenic and clastogenic and produced malignant transformation of rodent cells *in vitro*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 400
Trometamol (for pH adjustment)
Water for injections

6.2 Incompatibilities

Solutions of cytarabine have been reported to be incompatible with various drugs, i.e. carbenicillin sodium, cephalothin sodium, gentamicin sulphate, heparin sodium, hydrocortisone sodium succinate, insulin regular, methotrexate, 5-fluorouracil, nafcillin sodium, oxacillin sodium, penicillin G sodium (benzyl penicillin), methyl-prednisolone sodium succinate and prednisolone succinate.

However, the incompatibility depends on several factors (e.g. concentrations of the drug, specific diluents used, resulting pH and temperature). Specialised references should be consulted for specific compatibility information.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Solution for infusion or injection in unopened vial
2 years.

In-use shelf life of diluted solution
Chemical and physical in-use stability of the diluted solution has been demonstrated in 0.9% sodium chloride solution for infusion between 0.1 mg/ml and 21.6 mg/ml for up to 28 days at temperature below 25°C and for up to 28 days at 2-8° C.
Chemical and physical in-use stability of the diluted solution has been demonstrated in 5% glucose solution between 5.4 mg/ml and 21.6 mg/ml for up to 10 days at temperature below 25°C and for up to 28 days at 2-8°C. The diluted solutions do not require protection from light at 25°C storage conditions.

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 and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25ºC.

Do not refrigerate or freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless glass vial with rubber stopper coated with Fluorotec and an aluminium metallic cap with propylene disk. The vial may or may not be sheathed in a protective sleeve.

100 mg/1 ml (butyl, 3 ml nominal fill volume)
500 mg/5 ml (bromobutyl, 5 ml nominal fill volume)
1000 mg/10 ml (bromobutyl, 10 ml nominal fill volume)
2000 mg/20 ml (bromobutyl, 20 ml nominal fill volume)

Each pack contains 1 single−use vial.

Pack sizes:
1x 1 ml
1x 5 ml
1x 10 ml
1x 20 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

The undiluted/diluted solution should be clear, colourless to pale yellow and free from visible particles.

If the solution contains visible particles, it should be warmed to 55°C, for 30 minutes, with adequate shaking, and allowed to cool to room temperature.

Once opened, the contents of each vial must be used immediately. Discard any unused contents.

Cytarabine 100 mg/ml can be diluted with 0.9 % sodium chloride solution for infusion or 5% glucose solution (see section 6.3).

Cytotoxic handling guidelines

Administration
Cytarabine should be administered by, or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Preparation
- Chemotherapeutic agents should be prepared for administration only by professionals trained in the safe use of the preparation.
- Operations such as dilution and transfer to syringes should be carried out only in the designated area.
- The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.
- Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal and Contamination
To destroy, place in a high risk (for cytotoxics) waste disposal bag and incinerate at 1100°C.

If spills occur, restrict access to the affected area and adequate protection including gloves and safety spectacles should be worn. Limit the spread and clean the area with absorbent paper/material. Spills may also be treated with 5% sodium hypochlorite. The spill area should be cleaned with copious amounts of water. Place the contaminated material in a leak proof disposal bag for cytotoxics and incinerate at 1100ºC.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/041/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th February 2017

10 DATE OF REVISION OF THE TEXT