

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0705/001/001

Case No: 2048244

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Asta Medica Ltd

168 Cowley Road, Cambridge CB4 4DL, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Endoxana Injection 100 mg Powder for Solution for Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/05/2008** until **09/08/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Endoxana Injection 100 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cyclophosphamide monohydrate equivalent to 100 mg anhydrous cyclophosphamide.

When reconstituted as directed, the solution contains 20 mg cyclophosphamide per ml.

3 PHARMACEUTICAL FORM

Powder for solution for injection

A white crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Endoxana is a cytotoxic drug for the treatment of malignant disease in adults. As a single agent, it has successfully produced an objective remission in a wide range of malignant conditions. Endoxana is also frequently used in combination with other cytotoxic drugs, radiotherapy or surgery.

4.2 Posology and method of administration

Endoxana Injection is for intravenous administration.

Endoxana should only be used by clinicians experienced in the use of cancer chemotherapy. Endoxana should only be administered where there are facilities for regular monitoring of clinical, biochemical and haematological parameters before, during, and after administration and under the direction of a specialist oncology service.

Dosage

The dose, route of administration and frequency of administration should be determined by the tumour type, tumour stage, general condition of the patient and whether other chemotherapy or radiotherapy is to be administered concurrently.

A guide to the dosage regimens used for most indications is given below.

This treatment should be continued until a clear remission or improvement is seen or be interrupted when the extent of leucopenia becomes unacceptable.

Conventional: 80-300 mg/m² daily as single i.v. dose or daily divided oral doses.
 300-600 mg/m² as a single i.v. dose weekly.

High dose: 600-1500 mg/m² as a single i.v. dose or short infusion given at 10-20 day intervals.

Elderly: No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Children: The safety and effectiveness of Endoxana has not been established in children.

Administration

Endoxana is inert until activated by enzymes in the liver. However, as with all cytotoxics, it is suggested that reconstitution should be performed by trained personnel, in a designated area.

Those handling the preparation should wear protective gloves. Care should be taken to avoid splashing material into the eyes. The material should not be handled by women who are pregnant or who are breast-feeding.

For intravenous use, the contents of the vial should be dissolved in physiological saline (0.9% w/v sodium chloride) prior to administration. The pH of an aqueous solution is between 4 and 6. Endoxana is usually given directly into the tubing of a fast running i.v. infusion with the patient supine. Care should be taken that extravasation does not take place, however, should it occur, no specific measures need to be taken.

A minimum urine output of 100 ml/hour should be maintained during therapy with conventional doses to avoid cystitis. If the larger doses are used, an output of at least this level should be maintained for 24 hours following administration, if necessary by a forced diuresis.

Alkalisiation of the urine is not recommended. Endoxana should be given early in the day and the bladder voided frequently. The patient should be well hydrated and maintained in fluid balance.

Mesna (Uromitexan) can be used concurrently to reduce urotoxic effects (see Uromitexan SPC). If mesna (Uromitexan) is used to reduce urothelial toxicity, frequent emptying of the bladder should be avoided. Anti-emetics given before and during therapy may reduce nausea and vomiting.

Urine should be sent for laboratory analysis before and at the end of each course of treatment and the patient should be monitored for evidence of haematuria at regular intervals throughout the treatment period. The patient should be instructed to report any signs or symptoms of cystitis.

Endoxana Injection should be avoided in patients with cystitis from any cause until it has been treated.

If the leukocyte count is below $4 \times 10^9/\text{L}$ and / or the platelet count is below $100 \times 10^9/\text{L}$, treatment with Endoxana should be temporarily withheld until the blood count returns to normal levels.

4.3 Contraindications

Endoxana is contra-indicated in patients with known hypersensitivity to cyclophosphamide, with acute infections, with bone-marrow aplasia, urinary tract infection or with acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy.

Endoxana should not be used in the management of non-malignant disease, except for immuno-suppression in life-threatening situations.

Endoxana is contra-indicated during pregnancy.

4.4 Special warnings and precautions for use

Endoxana 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.

Care should be exercised in patients who are elderly, debilitated, have diabetes mellitus or evidence of myelosuppression, or who have recently received, or are receiving, concurrent treatment with radiotherapy or cytotoxic agents.

Cardiotoxicity may be induced in patients who have had, or are receiving, mediastinal irradiation, doxorubicin or pentostatin. It has also been reported with high doses of cyclophosphamide. In such instances cyclophosphamide therapy should be stopped and appropriate treatment instituted.

Endoxana is not recommended in patients with plasma creatinine greater than 120 micromol/L (1.5 mg/100 ml), bilirubin greater than 17 micromol/L (1 mg/100 ml), or with transaminases or alkaline phosphatase more than 2-3 times

the normal value.

Endoxana may have an adverse effect on the gonads and amenorrhoea and azoospermia often occur which may be irreversible. Appropriate counselling should be given.

4.5 Interaction with other medicinal products and other forms of interaction

Increased myelosuppression may be seen following concurrent administration of other marrow depressant drugs.

Endoxana potentiates the hypoglycaemic effects of the sulphonylurea compounds. Other clinically significant interactions are of cyclophosphamide with allopurinol (increased incidence of bone marrow depression) and suxamethonium (prolonged apnoea).

4.6 Pregnancy and lactation

Endoxana should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh the substantial risk to the foetus. Endoxana has been shown to be teratogenic. Mothers should not breast-feed while being treated with Endoxana.

4.7 Effects on ability to drive and use machines

A patient's ability to drive or operate machinery may be affected by the possible side effects of cyclophosphamide administration, e.g. nausea, vomiting.

4.8 Undesirable effects

Anorexia, nausea and vomiting and mucosal ulceration can occur. This may be reduced by the prior administration of an anti-emetic agent. Rarely renal and hepatic dysfunction (including jaundice and increased liver enzymes) have been reported.

Alopecia occurs to some degree in about 20% of patients receiving over 100 mg daily and is inevitable following high doses. Epilation commences usually after the first three weeks of treatment, but regrowth is evident after three months in most patients even though they remain on treatment.

The reticulo-endothelial system is depressed, granulopoiesis and lymphopoiesis being more affected than thrombopoiesis and erythropoiesis, but this depression is reversible. When a single dose is given, the fall in the peripheral white cell count reaches its nadir within 5-10 days. Recovery is seen at 10-14 days following administration, with full recovery in most cases by 21-28 days. The fall in the peripheral count and the time taken to recover may increase with increasing doses of Endoxana.

An alteration in carbohydrate metabolism may be seen in patients on Endoxana. Hyperglycaemia has been reported.

Azoospermia often occurs in men and is dose dependent. Spontaneous recovery of fertility may occur, and is also dependent on dose. Menstruation in women commonly ceases during therapy, and may be permanent, particularly in older women. Endoxana may have an adverse effect on prepubertal gonads.

Cardiotoxicity may be induced in patients who have had or are receiving mediastinal irradiation or doxorubicin. It has also been reported with high doses of cyclophosphamide. This mainly occurs as a tachyarrhythmia and may progress in severe cases to intractable heart failure. Following large doses, ECG changes and elevation of LDH (lactate dehydrogenase), AST (aspartate amino transferase) and CPK (creatine phosphokinase) have been reported in some patients.

Haematuria may occur during or after therapy with Endoxana. Where mesna (Uromitexan) is not given in conjunction with Endoxana, acute sterile haemorrhagic cystitis may occur in up to 10% of patients. Late sequelae of this cystitis are bladder contracture and fibrosis.

Endoxana has been shown to be mutagenic, teratogenic, and carcinogenic in certain laboratory tests and, as with other cytotoxic agents, there have been reports of possible drug-induced neoplasia. There is an excessive risk of acute leukaemia and bladder cancer following cyclophosphamide therapy.

Cyclophosphamide therapy may lead to inappropriate secretion of anti-diuretic hormone with fluid retention and hyponatraemia, and subsequent water intoxication.

In very rare cases, pneumonitis or interstitial pneumonia extending to chronic interstitial pulmonary fibrosis may develop. In particular, a late onset of pulmonary fibrosis may be irreversible and result in a fatal outcome.

Other side-effects, such as pancreatitis, pigmentation, macrocytosis, and induction of hyperglycaemia or hypoglycaemia have been reported.

Note:

There are certain complications, such as veno-occlusive disease, thromboembolism, DIC (disseminated intravascular coagulation) or haemolytic uraemic syndrome, that may also be induced by the underlying disease, but which might occur with an increased frequency during chemotherapy that includes Endoxana.

Side-effects have occasionally occurred after cessation of treatment.

4.9 Overdose

The most serious consequences of overdosage are myelosuppression, haemorrhagic cystitis and cardiotoxicity in the form of arrhythmias and severe heart failure. Myelosuppression usually recovers spontaneously, but until it does, administration of a broad-spectrum antibiotic may be advisable. Transfusion of whole-blood, platelets or white cells is rarely necessary.

If the overdose is recognised within the first 24 hours, and possibly up to 48 hours, i.v. Mesna may be beneficial in ameliorating damage to the urinary system. Normal supportive measures, such as analgesics and maintenance of fluid balance, should be instituted. If, despite these measures, the cystitis does not resolve, more intensive treatment may be necessary and a urological opinion should be sought. No further courses should be given until the patient has fully recovered.

Endoxana is dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cyclophosphamide is an antineoplastic agent which has been demonstrated to have a cytostatic effect in many tumour types. The active metabolites of cyclophosphamide are alkylating agents which transfer alkyl groups to DNA during the process of cell division, thus preventing normal synthesis of DNA.

5.2 Pharmacokinetic properties

Cyclophosphamide is well absorbed following an oral dose with a mean half-life of 4-8 hours for both oral and parenteral administration.

It is an inactive pro drug with alkylating metabolites produced by hepatic metabolism, reaching peak levels 4-6 hours after an i.v. injection. Hepatic enzymes may be induced. The parent compound binds poorly to plasma protein but the active metabolites are significantly protein-bound. The drug is widely distributed and crosses the blood-brain barrier, the placental barrier and is found in ascites. The metabolites are excreted renally.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to the information already stated in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Benzyl alcohol increases the degradation of cyclophosphamide.

6.3 Shelf Life

Unopened: 3 years.

After reconstitution for intravenous administration:

Chemical and physical in-use stability has been demonstrated (in aqueous, sodium chloride, and glucose solutions) for 48 hours at 2 – 8°C.

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 reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton.

After reconstitution store at 2-8°C and protect from light.

6.5 Nature and contents of container

20 ml type I or type III glass vial with butyl rubber closures and plastic and aluminium caps.

Pack size: 1 vial.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For intravenous administration

Prior to administration the contents of a vial should be dissolved in 5 ml Sodium Chloride 0.9 % w/v by introducing the saline into the vial and shaking vigorously until the powder is completely dissolved. Reconstitution results in a clear solution with pH of between 4 and 6.

For single use only. Discard any remaining contents.

Endoxana Injection is compatible with the following infusion solutions: sodium chloride, glucose solution, sodium chloride and glucose solution.

General instructions

If vials are stored above the recommended temperature this can cause degradation of the active ingredient, identifiable by a yellow melted appearance to the vial contents. Vials containing melted material should not be used.

Cyclophosphamide is a cytotoxic agent and should be treated accordingly. Protective gloves and appropriate equipment to protect against contact with eyes should be worn when handling the product. The material should not be handled by women who are pregnant or who are breast-feeding.

Adequate care and precautions should be taken in the disposal of empty vials and items (syringes, needles, etc) used in reconstitution and administration.

7 MARKETING AUTHORISATION HOLDER

ASTA Medica Limited
168 Cowley Road
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8 MARKETING AUTHORISATION NUMBER

PA 705/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 August 1990

Date of last renewal: 10 August 2005

10 DATE OF REVISION OF THE TEXT

December 2006