IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0048/022/005
Case No: 2035658

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

Bristol-Myers Squibb (Holdings)

Swords, **Co. Dublin**, **Ireland**

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

VEPESID Concentrate for Solution for Infusion 20mg/ml (5.0 ml Vial)

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 **17/04/2007** until **01/02/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vepesid Concentrate for Solution for Infusion 20 mg/ml (5.0 ml/vial).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml vial contains 100 mg etoposide (20 mg/ml).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
A clear, yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Vepesid is an anti-neoplastic drug for intravenous or oral use, which can be used alone or in combination with other oncolytic drugs.

Present data indicate that Vepesid is applicable in the therapy of: small cell lung cancer, resistant non-seminomatous testicular carcinoma.

4.2 Posology and method of administration

Adults:
The recommended course of Vepesid Injection is 60-120mg/m^2, i.v. daily for five consecutive days. As Vepesid produces myelosuppression, courses may not be repeated more frequently than at 21 day intervals. In any case, repeat courses of Vepesid should not be given until the blood picture has been checked for evidence for myelosuppression and found to be satisfactory.

Immediately before administration, the required dose of Vepesid Injection must be diluted with 0.9% saline solution for injection to give a solution concentration of not more than 0.25mg/ml of etoposide; it should then be given by intravenous infusion over a period of not less than 30 minutes.

Care should be taken to avoid extravasation.

Children:
Safety and effectiveness in children have not been established.

4.3 Contraindications

Vepesid is contra-indicated in patients with severe hepatic dysfunction or in those patients who have demonstrated hypersensitivity to the drug.

Vepesid must not be given by intra-cavitary injection

4.4 Special warnings and precautions for use

Vepesid should be administered by individuals experienced in the use of anti-neoplastic therapy.

When Vepesid is administered intravenously care should be taken to avoid extravasation.

If radiotherapy and/or chemotherapy has been given prior to starting Vepesid treatment, an adequate interval should be allowed to enable the bone marrow to recover. If the leucocyte count falls below 2000/mm^3, treatment should be suspended until the circulating blood elements have returned to acceptable levels (platelets above 100,000/mm^3, leucocytes above 4000/mm^3), this is usually within 10 days.

Peripheral blood counts and liver function should be monitored. (See Undesirable Effects.)

Bacterial infections should be brought under control before treatment with Vepesid commences.

The occurrence of acute leukaemia, which can occur with or without a preleukaemic phase has been reported rarely in patients treated with etoposide in association with other anti-neoplastic drugs.

Tumour lysis syndrome (sometime fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs. Close monitoring of patients is needed to detect early signs of tumour lysis syndrome, especially in patients with risk factors such as bulky treatment-sensitive tumours, and renal insufficiency. Appropriate preventive measures should also be considered in patients at risk of this complication of therapy.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

Vepesid is teratogenic in rats and mice at dose levels equivalent to those employed clinically. There are no adequate and well-controlled studies in pregnant women.

Vepesid should not normally be administered to patients who are pregnant or to mothers who are breast feeding. Women of childbearing potential should be advised to avoid becoming pregnant.

The influence of Vepesid on human reproduction has not been determined. *In-vitro* tests indicate that Vepesid is mutagenic.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Haematological: The dose limiting toxicity of Vepesid is myelosuppression, predominantly leucopenia and thrombocytopenia. Anaemia occurs infrequently. The leucocyte count nadir occurs approximately 21 days after treatment.

Alopecia: Alopecia occurs in approximately two-thirds of patients and is reversible on cessation of therapy.

Gastrointestinal: Nausea and vomiting are the major gastrointestinal toxicities and occur in over one-third of patients. Anti-emetics are useful in controlling these side-effects. Abdominal pain, anorexia, diarrhoea, oesophagitis and stomatitis occur infrequently.

Other Toxicities: Hypotension may occur following an excessively rapid infusion and may be reversed by slowing the infusion rate.

Anaphylactoid reactions have been reported following administration of Vepesid. Higher rates of anaphylactoid reactions have been reported in children who received infusions at concentrations higher than those recommended. The role that concentration of infusion (or rate of infusion) plays in the development of anaphylactoid reactions is uncertain. These reactions have usually responded to cessation of therapy and administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate.

Apnoea with spontaneous resumption of breathing following discontinuation of etoposide injection has been reported. Sudden fatal reactions associated with bronchospasm have been reported. Hypertension and/or flushing have also been reported. Blood pressure usually returns to normal within a few hours after cessation of the infusion.

The use of etoposide has been reported infrequently to cause peripheral neuropathy.

Vepesid has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment.

Somnolence, fatigue, aftertaste, fever, rash, pigmentation, pruritus, urticaria, dysphagia, transient cortical blindness and a single case of radiation recall dermatitis have also been reported following the administration of Vepesid.

Neoplasms benign, malignant and unspecified: Tumour lysis syndrome (sometimes fatal) has been reported very rarely (see Section 4.4 Special Warnings and Precautions for use).

4.9 Overdose

No proven antidotes have been established for Vepesid overdosage. Treatment should be symptomatic and supportive.

Total doses of 2.4 to 3.5 g/m^2 administered i.v. over three days have resulted in severe mucositis and myelotoxicity. Metabolic acidosis and cases of severe hepatic toxicity have been reported in patients receiving higher than recommended doses of etoposide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Etoposide is a semisynthetic derivative of podophyllotoxin.

Experimental data indicate that etoposide arrests the cell cycle in the G_2 phase. Etoposide differs from the vinca alkaloids in that it does not cause an accumulation of cells in the metaphase, but prevents cells from entering mitosis or destroys cells in the G_2 phase. The incorporation of the thymidine into DNA is inhibited in-vitro by etoposide. Etoposide does not interfere with microtubule assembly.

5.2 Pharmacokinetic properties

Etoposide is approximately 94% protein-bound in human serum. Plasma decay kinetics follow a bi-exponential curve and correspond to a two compartmental model. The mean volume of distribution is approximately 32% of body weight. Etoposide demonstrates relatively poor penetration into the cerebrospinal fluid.

Urinary excretion is approximately 45% of an administered dose, 29% being excreted unchanged in 72 hours.

5.3 Preclinical safety data

No further relevant data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Citric acid anhydrous
Ethanol
Macrogol 300
Polysorbate 80

6.2 Incompatibilities

None known.

6.3 Shelf Life

3 years.

Diluted infusion solution: After dilution as recommended to a concentration of 0.2 or 0.4 mg/ml, the infusion solution has been demonstrated to be physically and chemically stable at 25°C for 96 and 24 hours respectively.

From a microbiological point of view, the product should be used immediately after dilution. Other in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Unopened vials: Do not store above 25°C. Keep vials in the outer carton to protect from light.

6.5 Nature and contents of container

Type I flint glass vial with grey butyl rubber parenteral stopper and sealed with flip-off plastic/aluminium cap. Vials are packed in cartons containing ‘10 x 5 ml’ vials.

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

Preparation of Intravenous Solution:

Immediately before administration the required dose of Vepesid Injection must be diluted with 0.9% saline solution for injection to give a solution concentration of not more than 0.25 mg/ml of etoposide; it should then be given by intravenous infusion over a period of not less than 30 minutes. The infusion solution should be used immediately after dilution. Solutions of concentration greater than 0.25 mg/ml may show signs of precipitation, and are therefore not recommended. Any solutions showing signs of precipitation should be discarded.

The intravenous solution is suitable for infusion in glass or PVC containers.

Hard plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene and styrene) have been reported to crack and leak when used with undiluted Vepesid Injection. This effect has not been reported with diluted Vepesid Injection.

Vepesid should not be physically mixed with any other drug.

Guidelines for the Safe Handling of Antieoplastic Agents:

1. Trained personnel should reconstitute the drug.
2. This should be preformed in a designated area.
3. Adequate protective gloves should be worn.
4. Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or saline.
5. The cytotoxic preparation should not be handled by pregnant staff.
6. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1,000°C. Liquid waste may be flushed with copious amounts of water.
7. The work surface should be covered with disposable plastic-backed absorbent paper
8. Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may be reduced by the use of a venting needle.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Holdings Limited
t/a Bristol-Myers Pharmaceuticals
Swords
County Dublin

8 MARKETING AUTHORISATION NUMBER

PA 48/22/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd February 1989

Date of last renewal: 2nd February 2004

10 DATE OF REVISION OF THE TEXT

December 2004