SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Eldisine Powder for Solution for Injection 5.0 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eldisine Powder 5mg contains 5mg vindesine sulphate per 5ml when reconstituted.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for Solution for Injection

A clear glass vial containing a lyophilised plug of white crystalline powder.

4.1 Therapeutic Indications

Eldisine is an anti-neoplastic drug for intravenous use which can be used alone or in combination with other oncolytic drugs. Information available at present suggests that Eldisine as a single agent may be useful for the treatment of:

- acute lymphoblastic leukaemia of childhood resistant to other drugs;
- blastic crises of chronic myeloid leukaemia;
- malignant melanoma unresponsive to other forms of therapy;
- advanced carcinoma of the breast, unresponsive to appropriate endocrine surgery and/or hormonal therapy.

4.2 Posology and Method of Administration

This preparation is for intravenous use only. It should be administered only by individuals experienced in vindesine administration.

FOR INTRAVENOUS USE ONLY - FATAL IF GIVEN BY OTHER ROUTES

See special warnings in section 4.4 for the treatment of patients given intrathecal vindesine sulphate

Extreme care must be used in calculating and administering the dose of vindesine, since overdosage may have a very serious or fatal outcome.

It is recommended that the drug be administered intravenously in a single rapid bolus injection at weekly intervals. The size of the dose is determined by body surface area. In adults and the elderly, the recommended starting dose is 3mg/m^2, and children may be started at 4mg/m^2. Thereafter, granulocyte counts should be made prior to each subsequent dose to determine the patient's sensitivity to the drug. Provided there is no granulocytopenia or other toxicity (see 'Undesirable Effects') the dosage may be increased in 0.5mg/m^2 steps at weekly intervals.

In adults, the maximum total weekly dosage for which data exists is 4mg/m^2. The optimum dose of vindesine is that which produces mild to modest granulocytopenia. Sustained granulocyte counts lower than 2,500 cells/mm^3 are to be avoided.

Those with decreased marrow function from leukaemia infiltration or replacement will require full doses to attempt to restore marrow function. This must be done under close supervision.

The dose should not be increased after that dose which: (i) reduces the granulocyte count to below l500 cells/mm^3 or, on rare occasions, (ii) reduces the platelet count to below 100,000/mm^3; (iii) causes acute abdominal pain (see section 4.4).

On each of the above occasions there should be full recovery before administering the next dose, which should be reduced from the one causing the adverse reaction. For most patients, however, the weekly dosage will prove to be in the range of 3.0 to 4.0mg/m^2 in adults and 4.0 to 5.0mg/m^2 in children.

The use of small amounts of vindesine daily for long periods is not advised, even though the resulting total weekly dosage may be similar to that recommended. Little or no added therapeutic advantage has been demonstrated when such regimens have been used, and side effects are increased. Strict adherence to the recommended dosage schedule is very important.

As vindesine is excreted principally by the liver, it may be necessary to reduce initial doses in the presence of significantly impaired hepatic or biliary function.

The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes. (see section 4.5).

To prepare a solution containing 1mg/ml add 5ml of sterile 0.9% sodium chloride intravenous infusion to the 5mg of Eldisine in the sterile vial. The drug dissolves rapidly to give a clear solution.

The dose of Eldisine solution (calculated to provide the desired number of milligrams per square metre of the patient's surface area) may be injected either into the tubing of a running intravenous infusion *(compatible infusions are 5% Dextrose Intravenous Infusion BP, Sodium Chloride Intravenous Infusion BP and dextrose/saline infusions)* or directly into a vein.

The latter procedure is readily adaptable to outpatient therapy. In either case, the injection should be completed in 1 to 3 minutes. If care is taken to ensure that the needle is securely within the vein and that no solution containing vindesine is spilled extravascularly, cellulitis and/or phlebitis is unlikely to occur.

Because of the enhanced possibility of thrombosis, it is considered inadvisable to inject a solution into an extremity in which the circulation is impaired, or potentially impaired, by such conditions as compressing or invading neoplasm, phlebitis or varicosity.

Caution

It is extremely important to choose the largest accessible vein and to be certain that the needle is properly positioned in the vein before any vindesine is injected. If leakage into surrounding tissues should occur during intravenous administration, it may cause considerable irritation. The injection should be discontinued as soon as leakage occurs, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimise discomfort and the possibility of cellulitis.

4.3 Contra-indications

FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES

See special warnings in section 4.4 for the treatment of patients given intrathecal vindesine sulphate.

Use in patients who have drug-induced severe granulocytopenia (less than 1,500 granulocytes per mm^3) or severe thrombocytopenia.

Vindesine sulphate must not be used in the presence of severe bacterial infections. Such infections must be brought under control with antiseptics or antibiotics before using vindesine.

Patients with the demyelinating form of Charcot-Marie-Tooth syndrome should not be given vindesine.

Hypersensitivity to vindesine sulphate or to any of the excipients

4.4 Special Warnings and Precautions for Use

This preparation is for intravenous use only. It should be administered by individuals experienced in the administration of vindesine sulphate. The intrathecal administration of vindesine sulphate usually results in death. Syringes containing this product should be labelled "FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES." An auxiliary sticker is provided in the pack with this warning.

Extemporaneously prepared syringes containing this product must be packaged in an overwrap which is labelled "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES."

After inadvertent intrathecal administration of vinca alkaloids, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death. In a very small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards.

Based on the published management of survival cases involving the related vinca alkaloid vincristine sulphate, if vindesine is mistakenly given by the intrathecal route, the following treatment should be initiated **immediately after the injection:**

1. Removal of as much CSF as is safely possible through the lumbar access.

2. Insertion of an epidural catheter into the subarachnoid space via the intervertebral space above initial lumbar access and CSF irrigation with lactated Ringer's solution. Fresh frozen plasma should be requested and, when available, 25ml should be added to every 1 litre of lactated Ringer's solution.

3. Insertion of an intraventricular drain or catheter by a neurosurgeon and continuation of CSF irrigation with fluid removal through the lumbar access connected to a closed drainage system. Lactated Ringer's solution should be given by continuous infusion at 150ml/h, or at a rate of 75ml/h when fresh frozen plasma has been added as above.

The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150mg/dl.

The following measures have also been used in addition but may not be essential:

Glutamic acid has been given IV 10gm over 24 hours, followed by 500mg tds by mouth for 1 months. Folic acid has been administered intravenously as a 100mg bolus and then infused at a rate of 25mg/h for 24 hours, then bolus doses of25mg 6-hourly for 1 week. Pyridoxine has been given at a dose of 50mg 8-hourly by intravenous infusion over 30 minutes. Their roles in the reduction of neurotoxicity are unclear.

.Clinically, the dose-limiting toxicity of vindesine is granulocytopenia, although in general oncolytic activity is obtained at doses causing little or no effect on the granulocytes. Individual patient variation has been observed with respect to the severity of side-effects, including neurotoxicity, granulocytopenia, alopecia and decrease in bowel motility.

When granulocytopenia occurs, the nadir in the granulocyte count may be expected to occur 3-5 days after the last day of drug administration. Recovery of the granulocyte count is rapid thereafter and is usually complete within 7-10 days after the last dose.

The thrombocyte count is usually either unaffected or increased by weekly therapy with vindesine. However, significant thrombocytopenia has occurred occasionally, particularly when doses are given more frequently than once a week. It is probably more likely to occur when patients are thrombocytopenic (less than 100,000 cells/mm^3) prior to therapy with vindesine.

The effect of vindesine upon the red blood cell count and haemoglobin concentration is usually insignificant when other treatment does not complicate the picture. It should be remembered, however, that patients with malignant disease may exhibit anaemia even in the absence of any treatment.

If granulocytopenia with less than 1,000 granulocytes/mm^3 occurs following a dose of vindesine, the patient should be watched carefully for evidence of infection until the granulocyte count has returned to a safe level.

While neurotoxicity is not usually dose-limiting, there have been instances in which neurotoxicity has made it necessary to reduce the dosage or temporarily discontinue use of vindesine. Neurotoxicity induced by vindesine is believed to be generally less severe and less progressive in nature than the effects observed with vincristine.

Particular attention should be given to dosage and neurological side-effects if vindesine is administered to patients with pre-existing neuromuscular disease, and also when other drugs with neurotoxic potential are being used. The neurotoxicity associated with vindesine therapy may be additive.

Care should be exercised when vindesine has been the cause of acute abdominal pain, as paralytic ileus may be a significant risk if further doses of vindesine are given, particularly if the dose is increased. Prophylactic measures should be taken to prevent obstipation that may result from a decrease in bowel motility.

Extreme care should be exercised to prevent injection outside the vein. Extravasation during intravenous injection will cause cellulitis and phlebitis. If the amount of extravasation is great, sloughing will occur. Healing of such wounds may require several weeks and be attended by severe pain. The discomfort may persist after healing of the ulcer. Cytotoxic drugs should only be administered by appropriately trained staff.

Care must be taken to avoid contamination of the eye with concentrations of vindesine used clinically. If accidental contamination occurs, severe irritation and/or corneal ulceration may result. The eye should be washed immediately and thoroughly with water or saline.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

When chemotherapy is being given in conjunction with radiation therapy through portals, which include the liver, the use of vindesine should be delayed until radiation therapy has been completed.

Acute shortness of breath and severe bronchospasm have been reported following the administration of vindesine. These reactions have been encountered most frequently when vindesine was used in combination with mitomycinC and may be serious when there is pre-existing pulmonary dysfunction. The onset may be within minutes, or several hours after the drug is injected and may occur up to 2 weeks after a dose of mitomycinC. Progressive dyspnoea, requiring chronic therapy, may occur. Vindesine should not be re-administered.

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations have been reported to have reduced blood levels of the anticonvulsant and to have increased seizure activity. Although the contribution of the vinca alkaloids has not been established, dosage adjustment of phenytoin may need to be made when used in combination with vindesine.

Caution should be exercised in patients concurrently taking drugs shown to inhibit drug metabolism by hepatic cytochrome P450 isoenzyme in the CYP3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vindesine sulphate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects.

4.6 Fertility, Pregnancy and Lactation

Usage in pregnancy or lactation: The safety of this product for use during pregnancy has not been established. Animal studies with vindesine suggest that teratogenic effects may occur. The benefit-to-risk ratio must be carefully considered before use in pregnant patients.

Eldisine should not normally be given to mothers who are breast-feeding.

Men and women should be advised regarding contraception during treatment with vindesine due to the potential risks involved.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable Effects

Prior to the use of the drug, patients and/or their parents/guardians should be advised of the possibility of untoward symptoms. Acute toxicity appears to be dose related and is more likely to occur if doses above 4mg/m^2 are employed. Granulocytopenia is usually the dose limiting factor. Neurotoxicity is common and appears to be related to the cumulative total dose given.
The following side effects have been reported:
Gastro-intestinal: Nausea, vomiting, constipation, stomatitis, vesiculation of the mouth, ileus, diarrhoea, anorexia, abdominal pain, dysphagia, dyspepsia, perforated duodenal ulcer (nausea and vomiting usually may be controlled by anti-emetic agents).
Neurological: Numbness and tingling of hands/feet (paraesthesia), peripheral neuritis, jaw pain, mental depression, loss of deep tendon reflexes, foot drop, headache, convulsions. Cortical blindness has been reported in patients treated with multiple agent chemotherapy that has included vindesine. The contribution of vindesine to this reaction is unknown. Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness, which may be temporary or permanent, and difficulties with balance, including dizziness, nystagmus and vertigo. Particular caution is warranted when vindesine sulphate is used in combination with other agents known to be ototoxic, such as the platinum-containing oncolytics.
Haematological: Granulocytopenia, thrombocytopenia, thrombocytosis, mild anaemia.
Pulmonary: see section 4.5.

Cutaneous: Alopecia from mild to total is the commonest side effect. Regrowth of hair may occur while still on therapy. Maculopapular rashes, cellulitis with extravasation. Injection site reaction (see section 4.2).
Miscellaneous: Generalised musculoskeletal pain, malaise, chills and fevers, asthenia.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Side effects following the use of vindesine are dose related. Therefore, following administration of more than the recommended dose, patients can be expected to experience these effects in an exaggerated fashion.

Supportive care should include: (a) daily blood counts for guidance in transfusion requirement; (b) prevention of the side effects that result from the syndrome of inappropriate secretion of antidiuretic hormone. This includes restriction of fluid intake and, perhaps, the use of a diuretic drug acting on the loop of Henle and distal tubule function; (c) use of cathartics to prevent ileus; (d) administration of an anticonvulsant; (e) monitoring the patient's cardiovascular system.

The use of folinic acid in addition to the other supportive measures recommended may be considered although, unlike vincristine, studies have not been conducted to confirm its protective action. Clinical experience of vindesine overdosage is extremely limited, with only one published case.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Cytostatic agent from the group of vinca alkaloids; mitosis inhibitor. ATC code: L01CA03

Vindesine sulphate is an antineoplastic agent derived from vinblastine, like the other vinca alkaloids it causes mitotic arrest in metaphase by binding to microtubular protein.

5.2 Pharmacokinetic Properties

The pharmacokinetics of vindesine is similar to those of the other vinca alkaloids. After intravenous administration, elimination from the blood is triphasic, and the drug is rapidly distributed to body tissues. It is metabolised primarily in the liver and excreted in bile and urine.

5.3 Pre-clinical Safety Data

Animal studies with vindesine suggest that teratogenic effects may occur.

6 PHARMACEUTICAL PARTICULARS

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6.1 List of excipients

Mannitol
Sulphuric acid (diluted)
Sodium hydroxide (diluted).

6.2 Incompatibilities

Eldisine should never be mixed with any other drug.

6.3 Shelf-Life

5 years

6.4 Special Precautions for Storage

Vials of Eldisine should be stored in a refrigerator between 2° and 8°C.

After reconstitution: After a portion of the solution has been removed from a vial, the remainder of the contents of the vial may be stored in a refrigerator for future use for 24 hours without significant loss of potency. When the reconstituted vial of Eldisine is to be stored for more than 24 hours, it is essential to reconstitute with sterile 0.9% sodium chloride intravenous infusion preserved with 2.0% benzyl alcohol. Where preserved diluent is used, the reconstituted solution may be stored in a refrigerator for up to 28 days without significant loss of potency.

6.5 Nature and Contents of Container

Single vials comprising Type I glass each with a rubber stopper, an aluminium sealing ring and a polypropylene cap.

6.6 Instructions for Use and Handling

Guidelines for the safe handling of antineoplastic agents: Cytotoxic preparations should not be handled by pregnant staff.

Trained personnel should reconstitute the drug. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.

Adequate protective gloves, masks and clothing should be worn. Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. If accidental contamination occurs, the eye should be washed with water or saline thoroughly and immediately.

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 also be reduced by the use of a venting needle.

Adequate care and precaution should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic drugs.

Special dispensing information: When dispensing vindesine sulphate in other than the original container, e.g., a syringe containing a specific dose, it is imperative that it be packaged in an overwrap bearing the statement "DO NOT REMOVE COVER UNTIL MOMENT OF INJECTION. FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES". A syringe containing a specific dose must be labelled, using the auxiliary sticker provided in the pack, with this warning.

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PL 06831/0117

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

06/12/2023