Zavedos®

Powder for Injection

PHARMACIA

Idarubicin

Zavedos® (Idarubicin hydrochloride) is a new anthracycline antibiotic with antiblastic activity, synthesized in the Pharmacia Italia S.p.A. Laboratories.

Biological activity

Idarubicin is a DNA intercalating agent which interacts with topoisomerase II and has an inhibitory effect on nucleic acid synthesis.
The modification in position 4 of the anthracycline structure gives the compound a high lipophilicity which results in an increased rate of cellular uptake compared with doxorubicin and daunorubicin.
Idarubicin has been shown to have a higher potency with respect to daunorubicin and to be an effective agent against murine leukemia and lymphomas both by i.v and oral routes.
Studies ***in vitro*** on human and murine anthracyclines-resistant cells have shown a lower degree of cross-resistance for idarubicin compared with doxorubicin and daunorubicin.
Cardiotoxicity studies in animals have indicated that idarubicin has a better therapeutic index than daunorubicin and doxorubicin. The main metabolite, idarubicinol, has shown, ***in vitro*** and ***in vivo***, antitumoral activity in experimental models. In the rat, idarubicinol, administered at the same doses as the parent drug, is clearly less cardiotoxic than idarubicin.

Clinical pharmacology

After i.v administration to patients with normal renal and hepatic function, idarubicin is eliminated from systemic circulation with a terminal plasma $t_{1/2}$ ranging between 11-25h and is extensively metabolized to an active metabolite, idarubicinol, which is more slowly eliminated with a plasma $t_{1/2}$ ranging between 41 and 69h. The drug is eliminated by biliary and renal excretion, mostly in the form of idarubicinol.
Studies of cellular (nucleated blood and bone marrow cells) drug concentrations in leukemic patients have shown that peak cellular idarubicin concentrations are reached a few minutes after injection. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than a hundred times the plasma concentrations. Idarubicin disappearance rates in plasma and cells were almost comparable with a terminal half life of about 15h.
The terminal half life of idarubicinol in cells was about 72h.

Indications

Antimitotic and cytotoxic agent. Acute non-lymphocytic leukemia (ANLL) in adults for remission induction in untreated patients or for remission induction in relapsed or refractory patients.
Acute lymphocytic leukemia (ALL) as second line treatment in adults and children.

Administration

For reconstitution, the contents of the 5 mg vial should be dissolved in 5 ml of Water for Injections and the 10 mg vial in 10 ml of Water for Injections. Zavedos® must be administered only by the intravenous route and the reconstituted solution should be given via the tubing of a freely running intravenous infusion of 0.9% Sodium Chloride injection taking 5 to 10 minutes over the injections, after cheking that the needle is well placed in the vein. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and necrosis. Venous sclerosis may result from injection into small veins or repeated injections into the same vein.
Dosage is usally calculated on the basis of body surface area.

Dosage

Acute non-lymphocytic leukemia (ANLL)
In adult ANLL the dose schedule suggested is 12 mg/m² i.v. daily for 3 days in combination with cytarabine.
Another dose-schedule which has been used in ANLL as a single agent and in combination is 8 mg/m² i.v. daily for 5 days.
Acute lymphocytic leukemia (ALL)
As single agent in ALL the suggested dose in adults is 12 mg/m² i.v. daily for 3 days and in children is 10 mg/m² i.v. daily for 3 days.
All of these dosage schedules should, however, take into account the haematological status of the patient and the dosages of other cytotoxic drugs when used in combination.

Contraindications

Zavedos® therapy should not be started in patients with severe renal and liver impairment or patients with uncontrolled infections. See also "Use during Pregnancy and Lactation".

Warning

Zavedos® is intended for use under the direction of those experienced in leukemia chemotherapy. The drug should not be given to patients with pre-existing bone marrow suppression induced by previous drug therapy or radiotherapy unless the benefit warrants the risk. Pre-existing heart disease and previous therapy with anthracyclines at high cumulative doses or other potentially cardiotoxic agents are co-factors for increased risk of idarubicin-induced cardiac toxicity and the benefit to risk ratio of idarubicin therapy in such patients should be weighed before starting treatment with Zavedos®.
Like most other cytotoxic agents, idarubicin has mutagenic properties and it is carcinogenic in rats.

Bone Marrow
Zavedos® is a potent bone marrow suppressant. Myelosuppression, primarily of leukocytes, will therefore occur in all patients given a therapeutic dose of this agent and careful haematologic monitoring including granulocytes, red cells and platelets is required. Facilities with laboratory and supportive resources adequate to monitor drug tolerability and protect and maintain patient compromised by drug toxicity should be available. It must be possible to treat rapidly and effectively a severe hemorrhagic condition and/or a severe infection.

Cardiac Effects
Myocardial toxicity as manifested by potentially fatal congestive heart failure, acute life-threatening arrhythmias or other cardiomyopathies may occur during therapy or several weeks after termination of therapy. Treatment with digitalis, diuretics, sodium restriction and bed-rest is indicated.
Cardiac function should be carefully monitored during treatment in order to minimise the risk of cardiac toxicity of the type described for other anthracycline compounds. The risk of such myocardial toxicity may be higher following concomitant or previous

radiation to the mediastinal-pericardial area or treatment with other potentially cardiotoxic agents or in patients with a particular clinical situation due to their disease (anemia, bone marrow depression, infections, leukemic pericarditis and/or myocarditis).
While there is no reliable method for predicting acute congestive heart failure, cardiomyopathy induced by anthracyclines is usually associated with persistent QRS voltage reduction, increase beyond normal limits of the systolic time interval (PEP/LVET) and decrease of the left ventricular ejection fraction (LVET) from pretreatment baseline values.
An electrocardiogram or echocardiogram and a determination of left ventricular ejection fraction should be performed prior starting therapy and during treatment with Zavedos®. Early clinical diagnosis of drug-induced myocardial damage appears to be important for pharmacological treatment to be useful.

Evaluation of Hepatic and Renal Function
Since hepatic and/or renal function impairment can affect the disposition of idarubicin, liver and kidney function should be evaluated with conventional clinical laboratory tests (using serum bilirubin and serum creatinine as indicators) prior to, and during, treatment. In a number of Phase III clinical trials, treatment was not given if bilirubin and/or creatinine serum levels exceeded 2 mg%. With other anthracyclines a 50% dose reduction is generally employed if bilirubin and creatinine levels are in the range 1.2-2.0 mg%.

Precautions
Therapy with Zavedos® requires close observation of the patient and laboratory monitoring. Elderly patients should be given vigorous supportive treatment during the aplastic period. Hyperuricemia secondary to rapid lysis of leukemic cells may be induced: blood uric acid levels should be monitored and appropriate therapy initiated if hyperuricemia develops. Appropriate measures must be taken to control any systemic infection before beginning therapy.
Extravasation of Zavedos® at the site of i.v. injection can cause severe local tissue necrosis. The risk of thrombophlebitis at the injection site may be minimised by following the recommended procedure for administration.
A stinging or burning sensation at the site of administration signifies a small degree of extravasation and the infusion should be stopped and re-started in another vein.

Adverse reactions
Severe myelosuppression and cardiac toxicity are the two adverse effects. Other adverse reactions include: reversible alopecia in most patients; acute nausea and vomiting; mucositis, usually involving the oral mucosa and appearing 3-10 days after starting treatment; oesophagitis and diarrhoea; fever, chills, skin rash, elevation of liver enzymes and bilirubin in about 20-30% of cases. Severe and sometimes fatal infections have been associated with idarubicin alone or in combination with cytarabine. Idarubicin may impart a red colour to the urine for 1-2 days after administration and patients should be advised that this is no cause for alarm.

Use during pregnancy and lactation
There is no information as to whether idarubicin may adversely affect human fertility or cause teratogenesis. However, in rats (but not rabbits) it is teratogenic and embryotoxic. Women of child-bearing potential should be advised to avoid pregnancy. If Zavedos® is to be used during pregnancy or if the patient becomes pregnant during therapy, the patient should be informed of the potential hazard to the foetus. Therefore, the decision to use the drug in these situations must be taken jointly by doctor and patient.
Mothers should be advised not to breast-feed while undergoing chemotherapy with this drug.

Interactions
Zavedos® is a potent myelosuppressant and combination chemotherapy regimes which contain other agents having a similar action may be expected to lead to additive myelosuppresive effects.

Overdose
Very high doses of idarubicin may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression within one or two weeks. Treatment should aim to support the patient during this period and should utilise such measures as blood transfusion and reverse-barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to several months after the overdose. Patients should be observed carefully and if signs of cardiac failure arise, should be treated along conventional lines.

Pharmaceutical precautions
The vial contents are under negative pressure to minimise aerosol formation during reconstitution: particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided.
The following protective recommendations which are valid for all cytotoxic agents are given:
- personnel should be trained in good technique for reconstitution and handling;
- pregnant staff should be excluded from working with this drug;
- personnel handling the drug should wear protective clothing: goggles, gowns and disposable gloves and masks;
- a designated area should be defined for reconstitution (preferably under a vertical laminar flow system). The work surface should be disposable, plastic-backed, absorbent paper;
- all items used for reconstitution, administration or cleaning, incuding gloves, should be placed in high-risk waste disposal bags for high temperature incineration.

Accidental contact with the skin or eyes should be treated immediately by copious lavage with water: medical attention should be sought.
Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should subsequently be disposed of as indicated previously.
The reconstituted solution is chemically stable when stored for at least 48 hours at 2°-8°C and 24 hours at room temperature; however it is recommended that, in line with good pharmaceutical practice, the solution should not normally be stored for longer than 24 hours at 2°-8°C.
Discard any unused solution.
Prolonged contact with any solution of an alkaline pH should be avoided as it will result in degradation of the drug.
Zavedos® should not be mixed with heparin as a precipitate may form and it is not recommended that it is mixed with other drugs.

Presentation
5 mg and 10 mg vials for injection.

Keep out of the reach and sight of children.

Do not store above 25 °C. Do not refrigerate/freeze.

Medicinal product subject to medical prescription.

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