ZAVEDOS® CS

Idarubicin Hydrochloride Injection

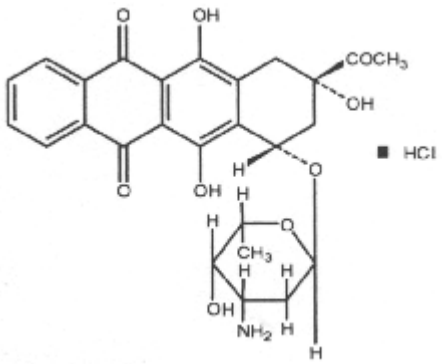
PRODUCT INFORMATION

Zavedos® CS (Idarubicin Hydrochloride), Solution for Injection (5 mg/5 mL & 10 mg/10 mL)

NAME OF THE MEDICINE

Non-proprietary name: Idarubicin Hydrochloride

The structural formula of idarubicin hydrochloride is shown below:



Chemical name: (7*S*,9*S*)-9-acetyl-7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-7-*O*-(2,3,6-trideoxy-3-amino-α-L-lyxo-hexopyranosyl)-5,12-naphthacenedione hydrochloride

CAS Registry Number: 57852-57-0

DESCRIPTION

Idarubicin hydrochloride is an odourless red-orange powder, slightly soluble in water, with a melting point of 173°C-174°C. The molecular formula is $C_{26}H_{27}NO_9 \cdot HCl$ and the molecular weight is 533.95.

Zavedos solution for injection consists of idarubicin hydrochloride as a red-orange, clear, mobile solution, free from particles.

PHARMACOLOGY

Pharmacodynamics

Zavedos is a semi synthetic antineoplastic anthracycline for intravenous use.

<u>Mechanism of action</u>

Idarubicin is a cytotoxic agent. It is a DNA intercalating agent which reacts with topoisomerase II and has an inhibitory effect on nucleic acid synthesis. The compound has a high lipophilicity which results in an increased rate of cellular uptake compared with doxorubicin and daunorubicin.

Pharmacodynamic effects

Idarubicin has been shown to have a higher potency with respect to daunorubicin and to be an effective agent against murine leukaemia and lymphomas. Studies *in vitro* on human and murine anthracycline-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 anti-tumour activities in experimental models both *in vitro* and *in vivo*. In the rat, idarubicinol, administered at the same doses as the parent drug, is less cardiotoxic than idarubicin.

Pharmacokinetics

After intravenous administration of idarubicin, there is triphasic disposition in plasma. Estimates of the plasma half-life for the parent compound range from 10 to 35 hours. Idarubicin is extensively metabolised to an active metabolite, idarubicinol, which has a plasma half-life ranging from 41 to 69 hours.

The plasma clearance is higher than the expected hepatic plasma flow, indicating extensive extrahepatic metabolism. Protein binding in plasma is 97% for idarubicin and 94% for idarubicinol. For both compounds, the binding is concentration independent.

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 elimination half-life in cells is about 15 hours and is similar to that in plasma. The elimination half-life for idarubicinol in cells is 72 hours.

Excretion takes place via the liver and kidneys, mainly in the form of idarubicinol. After intravenous administration of 13 mg/m^2 ^{14}C-idarubicin, 33% of the dose was excreted in urine and 39% in faeces after 14 days. Idarubicin excreted unchanged in urine accounts for 2%-7% of the dose, and idarubicinol, 9%-13%. In a patient with percutaneous biliary drainage, 17% of the dose was eliminated through the bile (as idarubicin plus idarubicinol) over five days.

Special populations

Renal impairment

Only limited information is available regarding the effect of an impaired renal function on the pharmacokinetics of idarubicin. A significant correlation is reported between the plasma clearance of idarubicin after intravenous dosing and creatinine clearance. In a study comparing patients with creatinine clearance <60 mL/min and those with normal creatinine clearance, idarubicin AUC was increased on average by 38% and idarubicinol AUC by 120% in the patients with reduced creatinine clearance; however, there was considerable variability.

Hepatic impairment

There is also limited information on the effect of impaired liver function on the pharmacokinetics of idarubicin. In a study comparing patients with liver metastases and mild liver impairment and those with normal liver function, there were no significant differences in idarubicin and idarubicinol pharmacokinetic parameters. However, in a patient with severe liver impairment, elimination of idarubicin was significantly delayed, the plasma elimination half-life being 112 hours.

INDICATIONS

Zavedos is indicated for use in acute myelogenous leukaemia (AML) in adults for remission induction in untreated patients or for remission induction in relapsed or refractory patients. Zavedos may be used in combination chemotherapy regimens involving other cytotoxic agents.

CONTRAINDICATIONS

Zavedos therapy is contraindicated in patients with severe renal and liver impairment or patients with uncontrolled infections. It should also not be administered to individuals with hypersensitivity to idarubicin or any other component of the product (see PRESENTATION AND STORAGE CONDITIONS) and/or other anthracyclines.

Zavedos therapy is contraindicated in patients with severe myocardial insufficiency, recent myocardial infarction, severe arrhythmias, persistent myelosuppression, or previous treatment with maximum cumulative doses of idarubicin and/or other anthracyclines and anthracenediones.

Zavedos therapy is contraindicated in pregnant women or women wishing to become pregnant (see PRECAUTIONS, Use in pregnancy (Category D)).

PRECAUTIONS

General

Zavedos is intended for use under the direction of those experienced in leukaemia chemotherapy. Close monitoring for toxicity is mandatory.

Facilities with laboratory and supportive resources adequate to monitor drug tolerability and protect and maintain a patient compromised by drug toxicity should be available. It must be possible to treat a severe haemorrhagic condition and/or severe infection rapidly and effectively.

The drug should not be given to patients with pre-existing bone marrow depression induced by previous drug therapy or radiotherapy unless the benefit warrants the risk.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropoenia, thrombocytopenia, and generalised infections) before beginning treatment with idarubicin.

Pre-existing heart disease and previous therapy with anthracyclines, especially at high cumulative doses, or other potentially cardiotoxic agents are co-factors for increased risk of idarubicin-induced cardiac toxicity: 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 is carcinogenic in rats.

Haematologic toxicity

Zavedos is a potent bone marrow suppressant. Myelosuppression, primarily of leucocytes, will therefore occur in all patients given a therapeutic dose of this agent and careful haematological monitoring including granulocytes, red cells and platelets is required.

Secondary leukaemia

Secondary leukaemia, with or without a pre-leukaemic phase, has been reported in patients treated with anthracyclines, including idarubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukaemias can have a 1- to 3-year latency period.

Cardiac function

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (acute) or late (delayed) events.

Early (acute) events

Early cardiotoxicity of idarubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities, such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity.

Late (delayed) events

Delayed cardiotoxicity usually develops late in the course of therapy or within 2 to 3 months after completion of treatment, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of CHF such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

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.

Idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative intravenous doses of 150 to 290 mg/m^2. Although cumulative dose limits are yet to be defined, available data on patients treated with Zavedos capsules indicate that total cumulative doses up to at least 400 mg/m^2 have a low probability of cardiotoxicity. Should congestive heart failure (CHF) occur, treatment with digitalis, diuretics, sodium restriction and bed rest is indicated.

Cardiac function should be monitored carefully during treatment in order to minimise the risk of cardiac toxicity of the type described for other anthracycline compounds. Risk factors for cardiac toxicity include concomitant or previous radiation to the mediastinal/pericardial area, previous treatment with other anthracyclines or anthracenediones at high cumulative doses, and concomitant use of drugs with the ability to suppress cardiac contractility or other potentially cardiotoxic agents (e.g., trastuzumab). Anthracyclines including idarubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see INTERACTIONS WITH OTHER MEDICINES). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab (variable half-life; washout period up to 7 months), may also be at an increased risk of developing cardiotoxicity.

Note: Trastuzumab emtansine has a shorter half-life of approximately 4 days. The half-life of trastuzumab is variable. Trastuzumab may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

The benefit to risk ratio of Zavedos therapy in such patients should be weighed before starting treatment. The risk of such myocardial toxicity may also be higher in patients with a pre-existing heart disease or particular clinical situation due to their disease (anaemia, bone marrow depression, infections, leukaemic 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/LET) and decrease of the LVEF from pre-treatment baseline values.

Assessment of cardiac function (evaluation of LVEF) with an ECG and either a multiple gated acquisition (MUGA) scan or an echocardiogram (ECHO) should be performed prior to starting therapy with Zavedos. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up. Early clinical diagnosis of drug-induced myocardial damage appears to be important for pharmacological treatment to be useful.

Gastrointestinal disorders

Severe enterocolitis with perforation has been reported rarely. The risk of perforation may be increased by instrumental intervention. The possibility of perforation should be considered in patients who develop severe abdominal pain and appropriate steps for diagnosis and management should be taken.

Hepatic and/or renal function

Since impairment of hepatic or renal function may 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. Idarubicin is contraindicated in severe hepatic and renal impairment. Also refer to DOSAGE AND ADMINISTRATION.

Tumour lysis syndrome

Idarubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells ('tumour lysis syndrome'). Blood uric acid levels, potassium, calcium, phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumour lysis syndrome. Appropriate measures must be taken to control any systemic infection before beginning therapy.

Effects at site of injection

With intravenous administered Zavedos, extravasation at the site of injection can cause pain, severe local tissue lesions (vesication, severe cellulitis) and necrosis. Extravasation may occur with or without accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If signs or symptoms of extravasation occur, the injection or infusion should be terminated immediately and restarted in another vein (see DOSAGE AND ADMINISTRATION).

Phlebosclerosis may result from an injection into a small vessel or from previous injections into the same vein.

Immunosuppressant effects/increased susceptibility to infections

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

Embryo-fetal toxicity

Idarubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with idarubicin. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available (see FERTILITY, PREGNANCY AND LACTATION and PRECLINICAL SAFETY DATA).

Other

Thrombophlebitis and thromboembolic phenomena, including pulmonary embolism, have been coincidentally reported with the use of idarubicin. The risk of thrombophlebitis at the injection site may be minimised by following the recommended procedure for administration.

FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Idarubicin can induce chromosomal damage in human spermatozoa. For this reason, males undergoing treatment with idarubicin should use effective contraceptive measures. Both men and women should seek advice on fertility preservation before treatment.

Use in pregnancy (Category D)

Zavedos should not be used during pregnancy (see CONTRAINDICATIONS).

There is no information as to whether idarubicin adversely affects fertility or causes teratogenesis in humans. However, it is teratogenic and embryotoxic in rats at intravenous doses of 0.7-1.4 mg/m^2/day. In rabbits, no evidence of teratogenicity was seen at the highest dose tested (2.2 mg/m^2/day, or one fifth of the human intravenous dose), which caused some maternal deaths. If the patient becomes pregnant during therapy, the patient should be informed of the potential hazard to the fetus.

Women of childbearing potential/contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant during treatment. Women of childbearing potential should be advised to use effective contraception during treatment with idarubicin and for at least 6.5 months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with idarubicin and for at least 3.5 months after the last dose.

Use in lactation

It is not known whether idarubicin or its metabolites are excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from idarubicin, advise lactating women not to breastfeed during treatment with idarubicin and for at least 14 days after last dose.

PRECLINICAL SAFETY DATA

Genotoxicity

Idarubicin was genotoxic in most of the *in vitro* or *in vivo* tests performed. Idarubicin was mutagenic *in vitro* in reverse mutation assays with *Salmonella typhimurium* and *Saccharomyces cerevisiae* D4. In forward mutation assays *in vitro*, idarubicin was mutagenic in Chinese Hamster V79 cells but not in *Schizosaccharomyces* pombe P1, either *in vitro* or *ex vivo*. Idarubicin was clastogenic in human lymphocytes and induced unscheduled DNA synthesis in rat hepatocytes *in vitro* and was clastogenic in the mouse micronucleus test *in vivo*.

Carcinogenicity

Long-term carcinogenicity studies have not been conducted with idarubicin, but like most other cytotoxic agents, idarubicin has mutagenic properties and is carcinogenic in rats. In male dogs, testicular atrophy with inhibition of spermatogenesis and sperm maturation was observed at threshold idarubicin doses 1.8 mg/m^2 administered intravenously (3 days/week for 13 weeks). These effects were not readily reversible after an eight-week recovery period.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of idarubicin on the ability to drive or use machinery has not been systematically evaluated. Special care should be taken if it is essential that patients drive or operate machinery while undergoing treatment with Zavedos, especially if in a debilitated condition.

INTERACTIONS WITH OTHER MEDICINES

Zavedos is a potent myelosuppressant and combination chemotherapy regimens which contain other agents having a similar action may be expected to lead to additive myelosuppressive effects, especially with regard to bone marrow/haematologic and gastrointestinal effects (see PRECAUTIONS).

The use of idarubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment (see PRECAUTIONS).

Changes in hepatic or renal function induced by concomitant therapies may affect idarubicin metabolism, pharmacokinetics, and therapeutic efficacy and/or toxicity (see PRECAUTIONS).

An additive myelosuppressant effect may occur when radiotherapy is given concomitantly or within 2-3 weeks prior to treatment with idarubicin.

ADVERSE EFFECTS

Severe myelosuppression and cardiac toxicity are the two major adverse effects. Most side effects are dose dependent, e.g., bone marrow depression and cardiotoxicity. All side effects except cardiomyopathy are reversible.

Adverse reactions that occur more frequently than 1% include:

Infections and infestations

Infection, sepsis/septicaemia.

Neoplasms benign, malignant and unspecified

Secondary leukaemias (acute myeloid leukaemia and myelodysplastic syndrome).

Immune system disorders

Anaphylaxis.

Blood and lymphatic system disorders

Anaemia, leucopenia, neutropenia, thrombocytopenia and bone marrow depression.

Gastrointestinal disorders

Abdominal pain or burning sensation, acute nausea and vomiting, mucositis/stomatitis, oesophagitis, diarrhoea, erosions/ulceration, gastrointestinal tract bleeding, colitis (including severe enterocolitis/neutropenic enterocolitis with perforation).

Skin and subcutaneous tissue disorders

Alopecia, skin rash/itch, acral erythema, hypersensitivity of irradiated skin (‘radiation recall reaction’), local toxicity, skin changes, skin and nail hyperpigmentation, urticaria.

Renal disorders

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.

Cardiac disorders

Cardiomyopathy, sinus tachycardia, tachyarrhythmias, atrioventricular and bundle branch block, subacute effects such as pericarditis/myocarditis.

Vascular disorders

Phlebitis, thrombophlebitis, thromboembolism, vasomotor instability (hot flushes), haemorrhage, shock.

Metabolism and nutrition disorders

Anorexia, dehydration, hyperuricaemia.

General disorders and administration site conditions

Fever, chills.

Investigations

Asymptomatic reductions in LVEF, ECG abnormalities, elevation of liver enzymes and bilirubin.

Description of selected adverse events

Myelosuppression

Haematological toxicity occurs in all patients receiving therapeutic doses of Zavedos and severe myelosuppression is the major toxicity associated with Zavedos therapy. Leucopenia is usually severe, with neutrophils as the white blood cell most significantly affected; thrombocytopenia and anaemia may also occur. During the period of myelosuppression, patients are at the risk of developing infection and bleeding which may be life threatening or fatal.

Leucocyte and platelet nadirs are usually reached 10 to 14 days following administration of the drug; however, cell counts generally return to normal levels during the third week.

Clinical consequences of bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death. Intravenous antibiotics should be given in the presence of febrile neutropenia.

Gastrointestinal disorders

Nausea and/or vomiting, mucositis (usually involving the oral mucosa and appearing 3-10 days after starting treatment), abdominal pain or burning sensation, diarrhoea and oesophagitis may occur but severe (WHO Grade 4) gastrointestinal toxicity is reported in less than 5% of patients.

Severe vomiting and diarrhoea may cause dehydration. Nausea and vomiting may be prevented or alleviated by the administration of appropriate antiemetic therapy.

Severe enterocolitis (neutropenic enterocolitis) with perforation has been reported. The possibility of perforation should be considered in patients who develop severe abdominal pain and appropriate steps for diagnosis and management should be taken.

Skin and subcutaneous tissue disorders

Alopecia is reported frequently and dermatological reactions including rash/itch, urticaria and a bullous erythrodermatous rash of the palms and soles can occur. The dermatological reactions are usually attributable to concomitant antibiotic therapy, skin changes, skin and nail hyperpigmentation, hypersensitivity of irradiated skin ('radiation recall reaction'), acral erythema, local toxicity and local reactions including hives at the injection site have been reported.

Cardiac disorders

As in the case of other anthracyclines, cardiac toxicity, as manifested by congestive heart failure (frequently attributed to fluid overload), serious life-threatening arrhythmias including atrial fibrillation, chest pain, myocardial infarction and asymptomatic declines in LVEF, have been reported in patients undergoing induction therapy for AML (see PRECAUTIONS). Myocardial insufficiency and arrhythmias are usually reversible and occur in the setting of sepsis, anaemia and aggressive intravenous fluid administration. The events were reported more frequently in patients over age 60 years and in those with pre-existing cardiac disease. Serious cardiac impairment may be prevented through regular surveillance during the course of treatment (see PRECAUTIONS). Subacute effects such as pericarditis/myocarditis have also been reported.

Hepatic and renal disorders

Changes in hepatic and renal function tests are severe (Grade 4) in less than 5% of patients, are usually transient and occur in the setting of sepsis and while patients are receiving potentially hepatotoxic and nephrotoxic antibiotics and antifungal agents.

DOSAGE AND ADMINISTRATION

Dose

For induction therapy in adult patients with AML, the following dose schedules are recommended:

Zavedos 12 mg/m^2 daily for three days by slow (10-15 min) intravenous injection in combination with cytarabine, 100 mg/m^2 daily given by continuous infusion for seven days. In patients with unequivocal evidence of leukaemia after the first induction course, a second course may be administered. Administration of the second course should be delayed in patients who experienced severe mucositis, until recovery from this toxicity has occurred, and a dose reduction of 25% is recommended.

Dosage adjustment

Hepatic and renal impairment

Zavedos should not be administered in patients with severe renal and liver impairment (see CONTRAINDICATIONS). Dose adjustment should be considered in patients with moderate liver and renal impairment (refer to Pharmacokinetics and PRECAUTIONS). With anthracyclines a 50% dose reduction is generally employed if bilirubin levels are in the range 1.2 to 2.0-mg %.

All dosage schedules should take into account the haematological status of the patient and all the doses of other cytotoxic drugs when used in combination.

Incompatibilities

Zavedos is not to be mixed with heparin since this causes precipitation, not to be mixed with alkaline solutions since this causes rapid degradation of Zavedos and it is not recommended that it be mixed with other drugs.

Method of administration

Intravenous infusion.

Zavedos solution for injection does not contains antimicrobial preservative. Use in one patient on one occasion only. Discard any residue.

Zavedos solution for injection must be administrated only by the intravenous route and should be given via tubing of a freely running intravenous infusion of 0.9% sodium chloride injection, taking 10-15 minutes over the injection.

The tubing should be attached to a butterfly needle or other suitable device and inserted preferably into a large 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 in the same vein.

Care in the administration of Zavedos will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking.

During intravenous administration of Zavedos, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs (½ hour immediately, then ½ hour 4 times per day for 3 days) be placed on the area of extravasation and that the affected extremity be elevated.

Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultations obtained early if there is any sign of local reaction such as pain, erythema, oedema or vesication. If ulceration begins or there is persistent pain at the site of extravasation, early wide excision of the involved area should be considered. Also refer to PRECAUTIONS, Effects at site of injection.

It is recommended that in order to reduce any microbiological hazards, further dilution be effected immediately prior to use and infusion be commenced as soon as practicable after preparation of the admixture. Infusion should be completed within 24 hours of preparation and any residue discarded.

Instructions for use and handling and disposal

Caution in handling of the solution must be exercised, as skin reactions associated with Zavedos may occur. Skin exposed accidentally to Zavedos should be washed thoroughly with water, soap and water or sodium bicarbonate solution and, if the eyes are involved, standard irrigation techniques should be used immediately. Medical attention should be sought. The following protective recommendations are given due to the toxic nature of the substance:

- Personnel should be trained in good technique for handling Zavedos.
- Pregnant staff should be excluded from working with Zavedos.
- The use of goggles, disposable masks and gloves and protective gowns are recommended during preparation and administration of the drug.
- A designated area should be defined for handling Zavedos (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed absorbent paper.
- All items used for administration or cleaning, including gloves should be placed in high-risk, waste-disposal bags for high temperature incineration.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as indicated previously.

OVERDOSAGE

Very high doses of idarubicin may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression within one or two weeks. Delayed cardiac failure has been seen with the anthracyclines up to several months after an overdose.

Two cases of fatal overdosage in patients receiving therapy for AML have been reported. The doses were 135 mg/m^2 over 3 days, and 45 mg/m^2 of idarubicin and 90 mg/m^2 of daunorubicin over a 3-day period.

There is no known antidote to Zavedos. Treatment should aim to support the patient and should utilise such measures as blood transfusions, reverse-barrier nursing, antibiotics and symptomatic treatment of mucositis.

Patients should be observed carefully and if signs of cardiac failure arise, should be treated along conventional lines.

Disposition studies with idarubicin in patients with severe renal failure or in those undergoing dialysis have not been carried out. The profound multi-compartment behaviour, extensive extravascular distribution and tissue binding, coupled with the low unbound fraction available in the plasma pool, make it unlikely that therapeutic efficacy or toxicity would be altered by conventional peritoneal haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

Zavedos solution for injection is supplied in single use only, polypropylene Cytosafe® vials:

5 mg/5 ml: The vial contains 5 mg of idarubicin hydrochloride, 125 mg glycerol, Water for Injections q.s. to 5 mL and hydrochloric acid to pH 3.5.

10 mg/10 ml: The vial contains 10 mg of idarubicin hydrochloride, 250 mg glycerol, Water for Injections q.s. to 10 mL and hydrochloric acid to pH 3.5.

Not all presentations may be marketed.

Storage conditions

Store at 2°C to 8°C. Refrigerate. Do not freeze. Protect from light.

MANUFACTURER

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