

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zavedos 10 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10mg idarubicin hydrochloride

The reconstituted solution contains 1mg/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Solution for Injection.

Orange-red, sterile, freeze-dried powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

For the treatment of acute non-lymphoblastic leukaemia (ANLL), for remission induction in untreated patients or for remission induction in relapsed or refractory patients.

For second line treatment of relapsed acute lymphoblastic leukaemia (ALL).

Children

For first line treatment of acute non-lymphoblastic leukaemia (ANLL), in combination with cytarabine, for remission induction.

For second line treatment of relapsed acute lymphoblastic leukaemia (ALL).

Zavedos may be used in combination chemotherapy regimens involving other cytotoxic agents (see section 4.2).

4.2 Posology and method of administration

For intravenous use only.

Not for intrathecal use.

Dosage is calculated on the basis of body surface area.

Acute non-lymphoblastic leukaemia (ANLL)

Adults

12 mg/m²/day i.v. daily for 3 days in combination with cytarabine.

or

8 mg/m²/day i.v. daily for 5 days with/without combination.

Children

10-12 mg/m² i.v. daily for 3 days in combination with cytarabine.

Acute lymphoblastic leukaemia (ALL)

Adults

As single agent in ALL the suggested dose in adults is 12 mg/m² i.v. daily for 3 days.

Children

10 mg/m² i.v. daily for 3 days, as a single agent.

NOTE: These are general guidelines. Refer to individual protocols for exact dosage.

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.

Administration of a second course should be delayed in patients who develop severe mucositis until recovery from this toxicity has occurred and a dose reduction of 25% is recommended.

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to idarubicin or to any of the excipients listed in section 6.1, other anthracyclines or anthracenediones
- Severe hepatic impairment
- Severe renal impairment
- Severe cardiomyopathy
- Recent myocardial infarction
- Severe arrhythmias
- Persistent myelosuppression
- Previous treatment with maximum cumulative doses of idarubicin hydrochloride and/or other anthracyclines and anthracenediones (see section 4.4)
- Breast-feeding should be stopped during drug therapy (see section 4.6)
- Uncontrolled infections

4.4 Special warnings and precautions for use

General

Idarubicin should be administered only under the supervision of physicians experienced in the use of cytotoxic chemotherapy. Therapy with Zavedos requires close observation of the patient and laboratory monitoring.

This ensures that immediate and effective treatment of severe complications of the disease and/or its treatment (e.g. haemorrhage, overwhelming infections) may be carried out.

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

Great caution should be exercised during the preparation and administration of Zavedos. Protective clothing and goggles should be worn by personnel. The solution should not be allowed to contact mucous membranes, eyes or skin of the patient.

Cardiac function

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. Appropriate treatment should be considered. 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 (anaemia, bone marrow depression, infection, leukemic pericarditis and/or myocarditis). Other risk factors included active or dormant cardiovascular disease, previous therapy with anthracyclines and anthracenediones and the concomitant use of drugs with the ability to suppress cardiac contractility.

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

Early (i.e. 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, are rarely of clinical importance, and are generally not a reason for the discontinuation of idarubicin treatment.

Late (i.e. delayed) events

Delayed cardiotoxicity usually develops late in the course of therapy or within 2 to 3 months after treatment termination, 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 congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly, 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.

On the basis of the recommended dosage schedules the total cumulative dose administered over two courses can be expected to reach 60 - 80 mg/m².

Cumulative dose limits for i.v or oral idarubicin hydrochloride have not been defined, a specific cardiological evaluation in cancer patients showed no significant modifications of cardiac function in patients treated with Zavedos at a mean cumulative dose of 93 mg/m². However, idarubicin -related cardiomyopathy was reported in 5% of patients who received cumulative i.v doses of 150 to 290 mg/m². Available data on patients treated with oral idarubicin hydrochloride total cumulative doses up to 400 mg/m² suggest a low probability of cardiotoxicity.

Early clinical diagnosis of drug-induced myocardial damage appears to be important for pharmacological treatment to be useful.

As with other anthracyclines, care must be taken when administering Zavedos to children because of the increased risk of cardiotoxicity from these products in the age group.

Cardiac function should be assessed before patients undergo treatment with idarubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of idarubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes Multiple Gated Acquisition (MUGA) scan or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. 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.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (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 section 4.5). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is variable. The substance may persist in circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If this is not possible, the patient's cardiac function should be monitored carefully.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with idarubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

In infants and children there appears to be a greater susceptibility to anthracycline induced cardiac toxicity, and a long-term periodic evaluation of cardiac function has to be performed. It is probable that the toxicity of idarubicin and other anthracyclines or anthracenediones is additive.

Haematologic toxicity

Idarubicin 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 haematological monitoring including granulocytes, red cells and platelets is required.

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.

Severe myelosuppression will occur in all patients given a therapeutic dose of this agent.

Haematologic profiles should be assessed before and during each cycle of therapy with idarubicin, including differential white blood cell (WBC) counts.

A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of idarubicin haematologic toxicity and is the most common acute dose limiting toxicity of this drug.

Leukopenia and neutropenia are usually severe; thrombocytopenia and anaemia may also occur. Neutrophil and platelet counts usually reach their nadir 10 to 14 days after drug administration; however, cell counts generally return to normal levels during the third week. During the phase of severe myelosuppression, deaths due to infections and/or haemorrhages have been reported.

Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death. . If febrile neutropenia occurs, treatment with an i.v antibiotic is recommended.

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 rapidly and completely a severe haemorrhagic condition and/or severe infection.

Patients aged over 55 years should be given vigorous supportive treatment during the aplastic period.

Secondary leukaemia

Secondary leukaemia, with or without a preleukemic 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 pretreated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukaemias can have a 1- to 3-year latency period.

Gastrointestinal

Idarubicin is emetigenic. Mucositis (mainly stomatitis, less often oesophagitis) generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Occasionally, episodes of serious gastrointestinal events (such as perforation or bleeding) have been observed in patients receiving oral idarubicin who had acute leukaemia or a history of other pathologies or had received medications known to lead to gastrointestinal complications. In patients with active gastrointestinal disease with increased risk of bleeding and/or perforation, the physician must balance the benefit of oral idarubicin therapy against the risk.

Carcinogenesis

Zavedos has mutagenic properties and it is carcinogenic in rats. Its carcinogenic potential in man is unknown. The possibility of a carcinogenic effect should be kept in mind in planning long-term therapy.

Hepatic and/or 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 contraindicated if bilirubin and/or creatinine serum levels exceeded 2.0-mg %. With other anthracyclines a 50% dose reduction is generally used if bilirubin levels are in the range 1.2 to 2.0-mg %.

Effects at site of injection

Phleboscrosis may result from an injection into a small vessel or from previous injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site.

Extravasation

Extravasation of idarubicin during intravenous injection may cause local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of idarubicin, the drug infusion should be immediately stopped and restarted in another vein.

In cases of extravasation dexrazoxane can be used to prevent or reduce tissue injury.

Tumour lysis syndrome

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

Immunosuppressant effects/increased susceptibility to infections

Administration of live or live-attenuated vaccines (like yellow fever) 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.

Reproductive system

Idarubicin can cause genotoxicity. Male and female patients treated with idarubicin hydrochloride are advised to adopt effective contraceptive measures during therapy and for a period after treatment.

Men treated with idarubicin hydrochloride are advised, if appropriate and available, to seek advice on sperm preservation due to the possibility of irreversible infertility caused by the therapy (see section 4.6). Patients desiring to have children after completion of therapy should be advised to discuss with an appropriate specialist first.

Other

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism have been coincidentally reported with the use of idarubicin.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

The product may cause a red colouration of the urine for 1 - 2 days after administration and patients should be advised of this fact.

4.5 Interaction with other medicinal products and other forms of interactions

Idarubicin is a potent myelosuppressant and combination chemotherapy regimens including other agents with similar action may be expected to induce additive myelosuppressive effects (see section 4.4).

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.

Changes in hepatic or renal function induced by concomitant therapies may affect idarubicin metabolism, pharmacokinetics, and therapeutic efficacy and/or toxicity (see section 4.4).

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

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 be mixed with other drugs.

Concomitant use of live attenuated vaccines (e.g. yellow fever) is not recommended, due to a risk of possibly fatal systemic disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. An inactivated vaccine should be used if available.

At combination of oral anticoagulants and anticancer chemotherapy, increased frequency of the INR (International Normalised Ratio) monitoring is recommended, since the risk for an interaction cannot be excluded.

Cyclosporin A: The co-administration of cyclosporin A as a single chemosensitizer significantly increased idarubicin AUC (1.78-fold) and idarubicinol AUC (2.46-fold) in patients with acute leukaemia. The clinical significance of this interaction is unknown.

A dosage adjustment may be necessary in some patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of idarubicin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Idarubicin should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus. The patient should be informed of the potential hazard to the foetus.

Women of childbearing potential/ Contraception in males and females

Women of child bearing potential should be advised not to become pregnant and 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 (see section 4.4).

Breast-feeding

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

Fertility

Idarubicin can induce chromosomal damage in human spermatozoa. For this reason, males undergoing treatment with idarubicin should use effective contraceptive methods for at least 3.5 months after the last dose (see section 4.4). Both men and women should seek advice on fertility preservation before treatment.

4.7 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.

4.8 Undesirable effects

The frequencies of undesirable effects are based on the following categories:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (frequency cannot be estimated from the available data)

Infections and infestations	
Very common	Infections
Uncommon	Sepsis, septicaemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Secondary leukaemia (acute myeloid

	leukaemia and myelodysplastic syndrome)
Blood and lymphatic system disorders	
Very common	Anaemia, severe leukopenia and neutropenia, thrombocytopenia
Not known	Pancytopenia
Immune system disorders	
Very rare	Anaphylaxis
Endocrine disorders	
Very common	Anorexia
Uncommon	Dehydration
Metabolism and nutrition disorders	
Uncommon	Hyperuricaemia
Not known	Tumour Lysis Syndrome
Nervous system disorders	
Rare	Cerebral haemorrhages
Cardiac disorders	
Common	Bradycardia, sinus tachycardia, tachyarrhythmia, asymptomatic reduction of left ventricular ejection fraction, congestive heart failure, cardiomyopathies (see section 4.4 for associated signs and symptoms)
Uncommon	ECG abnormalities (e.g. nonspecific ST segment changes), myocardial infarction
Very rare	Pericarditis, myocarditis, atrioventricular and bundle branch block
Vascular disorders	
Common	Local phlebitis, thrombophlebitis, haemorrhages
Uncommon	Shock
Very rare	Thromboembolism, flush
Gastrointestinal disorders	
Very common	Nausea, vomiting, mucositis/stomatitis, diarrhoea, abdominal pain or burning sensation
Common	Gastrointestinal tract bleeding, bellyache
Uncommon	Oesophagitis, colitis (including severe enterocolitis / neutropenic enterocolitis with perforation)
Very rare	Gastric erosions or ulcerations
Hepatobiliary disorders	
Common	Elevation of the liver enzymes and bilirubin
Skin and subcutaneous tissue disorders	
Very common	Alopecia
Common	Rash, itch, hypersensitivity of irradiated

	skin ('radiation recall reaction')
Uncommon	Skin and nail hyperpigmentation, urticaria, cellulitis (this event can be severe), tissue necrosis
Very rare	Acral erythema
Not known	Local reaction
Renal and urinary disorders	
Very common	Red coloration of the urine for 1 – 2 days after the treatment.
General disorders and administration site conditions	
Very common	Fever, headache, chills

Description of selected adverse reactions

Haematopoietic system

Pronounced myelosuppression is the most severe adverse effect of idarubicin treatment. However, this is necessary for the eradication of leukemic cells (see section 4.4).

Cardiotoxicity

Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug (see section 4.4).

Gastrointestinal

Stomatitis and in severe cases ulceration of mucosa, dehydration caused by severe vomiting and diarrhoea; risk of perforation of colon etc.

Administration site

Phlebitis/thrombophlebitis and prevention measures discussed in section 4.2; unintended paravenous infiltrates may cause pain, severe cellulites and tissue necrosis.

Other adverse reactions: hyperuricaemia

Prevention of symptoms by hydration, urine alkalinisation, and prophylaxis with allopurinol may minimise potential complications of tumour lysis syndrome.

Paediatric population

Undesirable effects are similar in adults and children except a greater susceptibility to anthracycline-induced cardiac toxicity of children (see section 4.4).

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Very high doses of idarubicin may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression within one to 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 treated with oral idarubicin should be observed for possible gastrointestinal haemorrhage and severe mucosal damage.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Idarubicin is a DNA intercalating agent which interacts with topoisomerase II and has an inhibitory effect on nucleic acid synthesis.

Idarubicin exhibits antitumour activity against murine leukaemia and lymphomas both by IV and oral route. In in vitro studies on human and murine anthracycline-resistant cells shows a low degree of cross-resistance for idarubicin compared with doxorubicin and daunorubicin.

The modification of 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 leukaemia and lymphomas both by IV and oral routes. 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 in-vitro and in-vivo antitumoural activity in experimental models.

In the rat, idarubicinol administered at the same doses as the parent drug, is clearly less cardiotoxic than Zavedos.

5.2 Pharmacokinetic properties

In adults, following oral administration of 10 to 60 mg/m² idarubicin, idarubicin was rapidly absorbed with the maximum plasma concentrations of 4-12.65 ng/mL achieved in 1 to 4 hours after dosing. The terminal half-life was 12.7±6.0 hrs (mean±SD). Following intravenous administration of idarubicin in adults, the terminal half-life was 13.9±5.9 hrs, similar to that observed after the oral administration.

After i.v. administration, idarubicin is extensively metabolised to an active metabolite, idarubicinol, which is slowly eliminated with a plasma T_{1/2} ranging between 41 - 69 hours). The drug is eliminated by biliary and renal excretion, mostly in the form of idarubicinol.

Studies of cellular (nucleated blood and bone marrow cells) in leukaemic 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 comparable, with a terminal half-life of about 15 hours. The terminal half-life of idarubicinol in cells was about 72 hours.

Paediatric population

Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin hydrochloride in doses ranging from 15 to 40 mg/m² over the 3 days of treatment, showed a median idarubicin half-life of 8.5 hrs (range: 3.6-26.4 hrs). The active metabolite, idarubicinol, accumulated during the 3 days of treatment, exhibiting a median half-life of 43.7 hrs (range: 27.8-131 hrs). In a separate study, pharmacokinetic measurements in 15 paediatric patients receiving oral idarubicin hydrochloride in doses ranging from 30 to 50 mg/m² during the 3 days of treatment, the maximum plasma concentration of idarubicin was 10.6 ng/mL (range 2.7-16.7 ng/mL at the 40 mg/m² dose). The median terminal half-life of idarubicin of was 9.2 hrs (range: 6.4-25.5 hrs). Significant accumulation of idarubicinol was seen over the 3 day treatment period. The observed terminal half-life value of idarubicin after i.v. was comparable to that following oral administration in paediatric patients.

Since C_{max} of idarubicin is similar in children and adults following oral administrations, absorption kinetics seem not to differ between adults and children.

Following both oral and i.v. administrations, the elimination half-life values of idarubicin in children and adults differ.

Total body clearance values of 30-107.9 L/h/m² for idarubicin reported for adults are higher than the values of 18-33 L/h/m² reported for paediatric populations. Although idarubicin has a very large volume of distribution in both adults and children, suggesting that much of the drug is bound to tissues, the shorter elimination half-life and lower total body clearance are not entirely explained by a smaller apparent volume of distribution in children compared to adults.

5.3 Preclinical safety data

Idarubicin has mutagenic properties and it is carcinogenic in rats.

Reproduction studies in animals have shown that idarubicin is embryotoxic and teratogenic in rats but not rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

6.2 Incompatibilities

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 be mixed with other drugs.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Unreconstituted solution: No special storage conditions.

Reconstituted solution: When aseptically prepared, the product may be stored for up to 24 hours at 2 °C to 8 °C. The product does not contain an antimicrobial preservative. Therefore if aseptic preparation cannot be ensured, the product must be prepared immediately before use and any unused portion discarded.

6.5 Nature and contents of container

Type I (Ph. Eur.) glass vial, sealed with a chlorobutyl rubber stopper. Zavedos 10 mg Powder for Solution for Injection vials are available as single 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

The following protective recommendations are given due to the toxic nature of this substance:

1. This product should be handled only by personnel who have been trained in the safe handling of such preparations.
2. Pregnant staff should be excluded from working with this drug.
3. Personnel handling Zavedos should wear protective clothing: goggles, gowns and disposable gloves and masks.
4. All items used for administration or cleaning, including gloves, should be placed in high risk, waste-disposal bags for high temperature incineration.
5. The reconstituted solution is hypotonic and the recommended administration procedure described below must be followed.

Reconstitute with 10 ml of Water for Injections to produce a 1mg/ml solution for injection (i.v.). The reconstituted solution is clear red-orange solution, essentially free from visible foreign matter, *see section 6.4.*

Intravenous administration: Zavedos, as the reconstituted solution, must be administered only by the intravenous route. A slow administration over 5 to 10 minutes via the tubing of a freely running intravenous infusion of 0.9% sodium chloride must be followed. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration, *see section 4.4*.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then with water.

All cleaning materials should be disposed of as indicated previously. Accidental contact with the skin and eyes should be treated immediately by copious lavage with water, or sodium bicarbonate solution, medical attention should be sought. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/142/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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