Idarubicin Hydrochloride Injection

ZAVEDOS®

1. GENERIC NAME

Idarubicin hydrochloride Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Idarubicin hydrochloride is available as:
Solution for injection containing Idarubicin hydrochloride U.S.P. 5 mg/5 mL

List of excipients

Solution for injection:
Glycerol
Water for injection
Hydrochloric acid (as 0.5 M)

3. DOSAGE FORM AND STRENGTH

Sterile solution for Injection

Strength: 5 mg/5 mL.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute non- lymphocytic leukaemia in adults for remission induction in untreated patients or for remission induction in relapse or refractory patients.

Acute lymphocytic leukaemia as second line treatment in adult and children.

4.2 Posology and method of administration

Posology

Acute lymphocytic leukemia (ALL)

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Adults
In monotherapy, the recommended dose is 12 mg/m^2 I.V. per day for 3 days.

Children
In monotherapy, the recommended dose is 10 mg/m^2 I.V. per day for 3 days.

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

It is, however, necessary to adapt the suggested dosages to the haematological conditions of the individual patient and, in combination regimens, to the dosage of the other cytotoxic drugs. Usually the dose is calculated on the basis of total body surface.

Method of administration

Zavedos (idarubicin hydrochloride) should be administered only by intravenous route (see section **8.4**).

The intravenous administration of the reconstituted solution should be carried out over a 5-10 minutes period through the tubing of an intravenous infusion of normal saline solution already in situ, after ascertaining that the needle is perfectly in the vein. This technique reduces the risk of thrombosis and perivenous overflow, events that could lead to serious problems of cellulitis or necrosis (see section **4.4**).

Venous sclerosis may be observed when the injection is carried out in small blood vessels or repeated into the same vein.

4.3 Contraindications

- Hypersensitivity to idarubicin or any other component of the product, listed in section **2**, 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 the therapy with idarubicin hydrochloride (see section **4.6**)

4.4 Special warnings and special precautions for use

General

idarubicin hydrochloride should be administered only under the supervision of physicians experienced in the use of cytotoxic chemotherapy.

This ensures that immediate and effective treatment of severe complications of the disease and/or its treatment (e.g., hemorrhage, 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.

Cardiac Function: 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 hydrochloride 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 hydrochloride 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.

Cumulative dose limits for IV or oral idarubicin hydrochloride have not been defined. However, idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative IV doses of 150 to 290 mg/m^2 of idarubicin. Available data on patients treated with oral idarubicin hydrochloride cumulative doses up to 400 mg/m^2 suggest a low probability of cardiotoxicity.

Cardiac function should be assessed before patients undergo treatment with idarubicin hydrochloride 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 hydrochloride 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 hydrochloride 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. It has been reported that trastuzumab has a variable half-life. 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.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with idarubicin hydrochloride 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 hydrochloride and other anthracyclines or anthracenediones is additive.

Haematologic Toxicity

Idarubicin hydrochloride is a potent bone marrow suppressant. Severe myelosuppression will occur in all patients given a therapeutic dose of this agent. Hematologic profiles should be assessed before and during each cycle of therapy with idarubicin hydrochloride, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of idarubicin hydrochloride hematologic 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. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death. If febrile neutropenia occurs, treatment with an IV antibiotic is recommended.

Secondary Leukaemia

Secondary leukaemia, with or without a pre-leukaemic phase, has been reported in patients treated with anthracyclines, including idarubicin hydrochloride. 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.

Gastrointestinal: Idarubicin hydrochloride is emetogenic. Mucositis (mainly stomatitis, less often esophagitis) 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 leukemia 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.

Hepatic and/or Renal Function: Since hepatic and/or renal function impairment can affect the disposition of idarubicin hydrochloride, 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: Phlebosclerosis may result from an injection into a small vessel or from previous injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see section **4.2**).

Extravasation: Extravasation of idarubicin hydrochloride 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 hydrochloride, the drug infusion should be immediately stopped. In cases of extravasation, dexrazoxane can be used to prevent or reduce tissue injury.

Tumour Lysis Syndrome

Idarubicin hydrochloride may induce hyperuricaemia 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 alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumour lysis syndrome.

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 hydrochloride. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Reproductive System: Idarubicin hydrochloride can cause genotoxicity. Men and women 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 should be advised that the product can cause red coloration of the urine for 1-2 days after administration.

4.5 Drug interactions

Idarubicin is a potent myelosuppressant and combination chemotherapy regimens including other agents with similar action may be expected to induce additive myelosuppressant effects (see section 4.4). The use of idarubicin in combination chemotherapy with other potentially cardiotoxic drugs (see section 4.4), 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.

Concomitant use with live attenuated vaccines (for example yellow fever) is not recommended due to the risk of a possible fatal systemic disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Use an inactivated vaccine where this exists (poliomyelitis).

At combination of oral anticoagulants and anticancer chemotherapy, increased frequency of the monitoring INR (International Normalised Ratio) 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 leukemia. The clinical significance of this interaction is unknown.

A dosage adjustment may be necessary in some patients.

4.6 Use in special population

Pregnancy:

There are limited amount of data from the use of idarubicin in pregnant women. Studies in animals and in vitro studies have shown reproductive toxicity (see section **6.1**). 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 childbearing 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**).

Lactation:

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 up to 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 (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (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 leukemia (acute myeloid leukemia and myelodysplastic syndrome)
<u>Blood and lymphatic system disorders</u>	
Very common	Anaemia, leukopenia, neutropenia, thrombocytopenia
Not known	Pancytopenia
<u>Immune system disorders</u>	
Very rare	Anaphylaxis
<u>Endocrine disorders</u>	
Very common	Anorexia
Uncommon	Dehydration
<u>Metabolism and nutrition disorders</u>	
Uncommon	Hyperuricemia
Not known	Tumour Lysis Syndrome
<u>Nervous system disorders</u>	
Rare	Cerebral haemorrhages
<u>Cardiac disorders</u>	
Common	Congestive heart failure, sinus tachycardia, tachyarrhythmia, asymptomatic reduction of left ventricular ejection fraction, bradycardia, 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
<u>Vascular disorders</u>	
Common	Haemorrhages, local phlebitis, thrombophlebitis
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	Esophagitis, 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, cellulites (This event can be severe), tissue necrosis
Very rare	Acral erythema
Unknown	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
Common	Haemorrhages
Uncommon	Dehydration

Description of selected adverse reactions

Hematopoietic system
Pronounced myelosuppression is the most serious side effect. 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**; paravenous unintended 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 tumor 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**).

4.9 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. Delayed cardiac failure has been seen with the anthracyclines up to several months after an overdose.

Patients treated with oral idarubicin should be observed for possible gastrointestinal haemorrhage and severe mucosal damage.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of action

Pharmaco-therapeutic Group: cytotoxic antibiotics – anthracyclines.

ATC Code: L01DB06

Idarubicin is a DNA intercalating anthracycline that interacts with the topoisomerase II enzyme and has an inhibitory effect on the synthesis of nucleic acid.

The change in position 4 of the structure of the anthracycline gives the compound a high level of lipophilicity with a subsequent increase in penetration within the cell compared to doxorubicin and daunorubicin.

5.2 Pharmacodynamic properties

Idarubicin has been found to be more powerful than daunorubicin and to be a more effective agent against leukaemia and murine lymphomas both by intravenously and when given orally. *In vitro* studies on murine and human anthracycline-resistant cells have shown a lower rate of cross-resistance for idarubicin than for doxorubicin or daunorubicin. Studies of cardiotoxicity in animals have indicated that idarubicin has a better therapeutic index than daunorubicin and doxorubicin. The main metabolite, idarubicinol, too, has shown anti-tumour activities in experimental models, both *in vitro* and *in vivo*. When administered to rats, at the same doses as the drug from which it is derived, idarubicinol, is clearly less cardiotoxic than idarubicin.

5.3 Pharmacokinetic properties

Following intravenous administration in patients with normal liver and kidney function, idarubicin is eliminated from the general circulation with a plasmatic half-life of 11-25 hours.
The drug is for the main part converted to an active metabolite, idarubicinol, which is slowly eliminated with a plasmatic half-life of 41-69 hours.
The drug is eliminated by means of biliary and renal excretion, mainly in the form of idarubicinol.

Studies on the concentration of the drug in the cells (nucleated blood cells and bone marrow cells) of leukemic patients have shown that the peak of cellular concentration for idarubicin is reached in just a few minutes. The concentrations of idarubicin and idarubicinol in the nucleated blood cells and in the bone marrow cells are more than one hundred times greater than the concentrations in the plasma. The speeds of elimination from the plasma and from the cells are almost identical, with a terminal halving time of around 15 hours. The terminal half-life of idarubicinol is 72 hours.

Paediatric population
Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin in doses ranging from 15 to 40 mg/m^2 for 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/m^2 during the 3 days of treatment, the maximum plasma concentration of idarubicin hydrochloride was 10.6 ng/mL (range 2.7-16.7 ng/mL at the 40 mg/m^2 dose). The median terminal half-life of idarubicin hydrochloride was 9.2 hrs (range: 6.4-25.5 hrs). Significant accumulation of idarubicinol was seen over the 3 days treatment period. The observed terminal half-life value of idarubicin hydrochloride after IV was comparable to that following oral administration in paediatric patients.

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

Following both oral and IV administrations, the elimination half-life values of idarubicin hydrochloride in children and adults differs.

Total body clearance values of 30-107.9 L/h/m^2 for idarubicin reported for adults are higher than the values of 18-33 L/h/m^2 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.

6. NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology

Following intravenous administration of idarubicin hydrochloride to mice, the LD_{50} value is 4.4 mg/kg in mice, 2.9 mg/kg in rats and 1.0 mg/kg in dogs. The main target organs after the administration of a single dose have been found to be the haemolymphopoietic system and, especially in dogs, the gastrointestinal tract.

The main target organs, after the repeated administration of idarubicin by intravenous route to rats and dogs, have been found to be the haemolymphopoietic system, the gastrointestinal tract, the kidneys, the liver and both the male and female reproductive organs.

Studies of acute and subacute cardiotoxicity have revealed that idarubicin, administered intravenously, is moderately cardiotoxic only at lethal doses, while intravenous administrations of doxorubicin and daunorubicin determine evident myocardial damage even at non-lethal doses.

Idarubicin has proved to be genotoxic in the majority of the tests carried out both *in vitro* and *in vivo*. It has also proved toxic on the reproductive organs, embryotoxic and teratogenic in rats. No relevant effects have been reported on the mothers or their offspring in rats after the intravenous administration of idarubicin at doses of 0.2 mg/kg/day in the peri- and post-natal period.

It is not known whether the drug is excreted in the mother's milk. Idarubicin by intravenous route, like other anthracyclines and cytotoxic drugs, has proved carcinogenic in rats.

A study of local tolerability conducted on dogs has shown that extravasation of the drug causes necrosis of the tissues.

7. DESCRIPTION

Solution for injection: Plastic vials containing a red-orange, clear, mobile solution free from particles

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

Idarubicin should not be mixed with other drugs. Contact with any solution of an alkaline pH should be avoided as it will result in degradation of the drug. Idarubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

8.2. Shelf-life

36 months

8.3. Packaging information

Solution for injection:
Polypropylene vial

8.4. Storage and handling instruction

Solution for injection:

Store between 2°C to 8°C. Protect from light.

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 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, including 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.

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.

Instructions for Use and Handling and Disposal

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 reconstitution and handling.
- 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 reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed absorbent paper.
- All items used for reconstitution, 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.

9. PATIENT COUNSELLING INFORMATION

- ZAVEDOS (idarubicin hydrochloride for injection, USP) should be given slowly into a freely flowing intravenous infusion. It must never be given intramuscularly or subcutaneously. Severe local tissue necrosis can occur if there is extravasation during administration.
- As is the case with other anthracyclines the use of ZAVEDOS can cause myocardial toxicity leading to congestive heart failure. Cardiac toxicity in patients who have received prior anthracyclines or who have preexisting cardiac disease.
- Severe myelosuppression occurs when ZAVEDOS is used at effective therapeutic doses.
- It is recommended that ZAVEDOS be administered only under the supervision of a physician who is experienced in cytotoxic chemotherapy and in facilities with laboratory and supportive resources adequate to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The physician and institution must be capable of responding rapidly and completely to severe hemorrhagic conditions and/or overwhelming infection.
- Patients with impaired hepatic or renal function should be closely monitored as the deposition of Zavedos may be affected in these patients. (see section 4.4).
- Zavedos should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus. (See Section 4.6)
- Women of childbearing potential should be advised not to become pregnant and to use effective contraception during treatment with Zavedos 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 4.6)
- Because of the potential harm to the infant, mothers should be advised to avoid breastfeeding while receiving Zavedos and for at least 14 days after the last dose (see section 4.6).
- Both men and women should seek advice on fertility preservation before treatment (see sections 4.6).

10. DETAILS OF MANUFACTURER

MANUFACTURED BY

Solution for Injection: M/s. Bridgewest Perth Pharma Pty. Ltd, 15 Brodie Hall Drive, Bentley, Western Australia 6102, Australia

IMPORTED AND MARKETED IN INDIA BY

Pfizer Products India Private Limited, The Capital- B Wing, 1802, 18th Floor, Plot No. C-70, G-Block, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

FF-328-6803 dated 16-May-2023* (*The license is renewed every 3 years as per regulations).

12. DATE OF REVISION

July 2023