IDARUBICIN

ZAVEDOS®

5 mg Lyophilized Powder for IV Injection

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1.0 PHARMACOLOGIC CATEGORY

Antineoplastic (Anthracycline and related substance)

2.0 DESCRIPTION

Lyophilized Powder for IV Injection.

Sterile, pyrogen-free, orange-red, freeze-dried powder in vial containing 5 mg of Idarubicin hydrochloride, with 50 mg of lactose monohydrate.

3.0 FORMULATION/ COMPOSITION

Each vial contains:
Idarubicin hydrochloride……5 mg
Reconstituted solution contains 1 mg/mL.

Lactose monohydrate.……50 mg

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults
For the treatment of acute myeloid leukemia (AML), for remission induction in untreated patients or for remission induction in relapsed or refractory patients.

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

Children
For first line treatment of acute myeloid leukemia (AML), in combination with cytarabine, for remission induction.

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

Idarubicin (Zavedos®) may be used in combination chemotherapy regimens involving other cytotoxic agents (see **section 4.2 Dosage and Method of Administration**).

4.2 Dosage and Method of Administration

For intravenous use only.
Not for intrathecal use.

Dosage is calculated on the basis of body surface area.

Acute myeloid leukemia (AML)

Adults
12 mg/m^2/day I.V. daily for 3 days in combination with cytarabine.
or
8 mg/m^2/day I.V. daily for 5 days with/without combination.

Children
10-12 mg/m^2 I.V. daily for 3 days in combination with cytarabine.

Acute lymphoblastic leukemia (ALL)

Adults
As single agent in ALL the suggested dose in adults is 12 mg/m^2 I.V. daily for 3 days.

Children
10 mg/m^2 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 hematological 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 6.4. Special Precautions for Disposal and Other Handling**.

4.3 Contraindications

- Hypersensitivity to Idarubicin or to other anthracyclines or anthracenediones
- Severe hepatic impairment
- Severe renal impairment
- Uncontrolled infections
- Severe cardiomyopathy
- Recent myocardial infarction
- Severe arrhythmias
- Persistent myelosuppression

- Previous treatment with maximum cumulative doses of Idarubicin and/or other anthracyclines and anthracenediones (see **section 4.4 Special Warnings and Precautions for Use**).
- Breast-feeding should be stopped during drug therapy (see **section 4.6 Fertility, Pregnancy and Lactation**)

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.

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.

Hematological toxicity
Idarubicin is a potent bone marrow suppressant. Severe myelosuppression, will occur in all patients given a therapeutic dose of this agent.

Hematological 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 hematologic toxicity and is the most common acute dose limiting toxicity of the drug.

Leukopenia and neutropenia are usually severe, thrombocytopenia and anemia 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 hemorrhages have been reported.

Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia or death. If febrile neutropenia occurs, treatment with an I.V. antibiotic is recommended.

Secondary leukemia
Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including Idarubicin. Secondary leukemia 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 leukemias can have a 1 to 3-year latency period.

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 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 dyspnea, pulmonary edema, dependent edema, 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 I.V. or oral Idarubicin have not been defined. However, Idarubicin related cardiomyopathy was reported in 5% of patients who received cumulative I.V. doses of 150 to 290 mg/m^2. Available data on patients treated with oral Idarubicin total 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 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 Interaction with Other Medicinal Products and Other Forms of Interaction**). 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.

Hepatic and renal function

Since hepatic and/or renal function impairment can affect the disposition of Idarubicin, liver and kidney function should be evaluated with conventional clinical laboratory tests (using serum bilirubin and serum creatinine as indicators) prior to, and during, treatment. In a number of Phase III clinical trials, treatment was 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 - 2.0 mg%.

Gastrointestinal

Idarubicin 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.

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.

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.

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

Tumor lysis syndrome
Idarubicin may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells ('tumor lysis syndrome'). Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor lysis syndrome.

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 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 Fertility, Pregnancy and Lactation**). 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 coloration 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 Interaction

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 Special Warnings and Precautions for Use**).

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 Special Warnings and Precautions for Use**).

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.

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

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 Normalized 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 leukemia. 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 Preclinical Safety Data**). Idarubicin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. 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 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 Special Warnings and Precautions for Use**).

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. 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 (frequency cannot be estimated from the available data)

Infections and infestations	
Very Common	Infections

Uncommon	Sepsis, Septicemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Secondary Leukemia (Acute Myeloid Leukemia and Myelodysplastic Syndrome)
Blood and lymphatic system disorders	
Very Common	Anemia, 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	Hyperuricemia
Not Known	Tumor Lysis Syndrome
Nervous system disorders	
Rare	Cerebral Hemorrhages
Cardiac disorders	
Common	Bradycardia, Sinus Tachycardia, Tachyarrhythmia, Asymptomatic Reduction of Left Ventricular Ejection Fraction, Congestive Heart Failure, Cardiomyopathies (See **Section 4.4 Special Warnings and Precautions for Use** 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, Hemorrhages
Uncommon	Shock
Very Rare	Thromboembolism, Flush
Gastrointestinal disorders	
Very Common	Nausea, Vomiting, Mucositis/Stomatitis, Diarrhea, 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, 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

Hematopoietic 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 Special Warnings and Precautions for Use**).

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 Special Warnings and Precautions for Use**).

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

Administration site
Phlebitis/thrombophlebitis and prevention measures discussed in section **4.2 Dosage and Method of Administration**; unintended paravenous infiltrates may cause pain, severe cellulites and tissue necrosis.

Other adverse reactions: hyperuricemia
Prevention of symptoms by hydration, urine alkalinization, and prophylaxis with allopurinol may minimize potential complications of tumor lysis syndrome.

Pediatric population
Undesirable effects are similar in adults and children except a greater susceptibility to anthracycline-induced cardiac toxicity of children (see **section 4.4 Special Warnings and Precautions for Use**).

4.9 Overdose and Treatment

Very high doses of Idarubicin may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression within one to two weeks. Delayed

cardiac failure has been seen with the anthracyclines for up to several months after the overdose. Patients treated with oral Idarubicin should be observed for possible gastrointestinal hemorrhage and severe mucosal damage.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Anthracyclines and related substances
ATC Code: L01DB06

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

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 leukemia and lymphomas both by I.V. 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,* antitumoral activity in experimental models. In the rat, idarubicinol administered at the same doses as the parent drug, is clearly less cardiotoxic than Idarubicin.

In vitro studies have shown plasma protein binding of at least 95% for this product. This fact should be borne in mind when considering its use in combination with other drugs.

5.2 Pharmacokinetic Properties

In adults, following oral administration of 10 to 60 mg/m^2 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 T½ ranging between 41 - 69 hours. The drug is eliminated by biliary and renal excretion, mostly in the form or idarubicinol.

Studies of cellular (nucleated blood and bone marrow cells) in leukemic patients have shown that peak cellular Idarubicin concentrations are reached a few minutes after injection.

Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than a hundred times the plasma concentrations. Idarubicin disappearance rates in plasma and cells were comparable, with a terminal half-life of about 15 hours. The terminal half-life of idarubicinol in cells was about 72 hours.

Pediatric population

Pharmacokinetic measurements in 7 pediatric patients receiving intravenous Idarubicin hydrochloride in doses ranging from 15 to 40 mg/m^2 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 pediatric patients receiving oral Idarubicin in doses ranging from 30 to 50 mg/m^2 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/m^2 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 pediatric 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/m^2 for Idarubicin reported for adults are higher than the values of 18-33 L/h/m^2 reported for pediatric 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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date.

6.2 Storage Conditions

Unreconstituted solution
Store at temperatures not exceeding 30°C.

Reconstituted solution
The reconstituted solution is chemically stable when stored for at least 48 hours at 2-8°C and 24 hours at 28-32°C; however, it is recommended that, in line with good pharmaceutical practice, the solution should not normally be stored for longer than 24 hours at 2-8°C.

The product does not contain any antibacterial preservative. Therefore, if aseptic preparation cannot be ensured, the product must be prepared immediately before use and any unused portion discarded.

6.3 Availability

5 mg Lyophilized Powder for IV Injection - 10 mL - Capacity Type I Colorless Glass Vial with Chlorobutyl Rubber Stopper and Aluminum Seal with Polypropylene Flip-off Top (Box of 1's).

6.4 Special Precautions for Disposal and Other Handling

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

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

Reconstitute with 5 mL of Water for Injections to produce a 1 mg/mL solution for IV injection. The reconstituted solution is clear red-orange solution, essentially free from visible foreign matter, see **section 6.2 Storage Conditions** also.

Intravenous administration: Idarubicin (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 Special Warnings and Precautions for Use**).

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.

6.5 Incompatibilities

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in degradation of the drug. Idarubicin (Zavedos®) should not be mixed with heparin as a precipitate may form and it is not recommended that it be mixed with other drugs.

7.0 FDA REGISTRATION NUMBER

5 mg Lyophilized Powder for IV Injection - DR-XY15884

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

5 mg Lyophilized Powder for IV Injection - 20 May 1993

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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