ZAVEDOS®
(Idarubicin hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

ZAVEDOS®.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains freeze dried powder of Idarubicin hydrochloride 5 mg or 10 mg.

3. PHARMACEUTICAL FORM

Freeze dried powder for solution for injection.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

ZAVEDOS® (Idarubicin hydrochloride) is an antimitotic and cytotoxic agent commonly used in combination chemotherapy regimens involving other cytotoxic agents. Idarubicin hydrochloride is indicated for treatment of the following cancers:

- Acute non-lymphocytic leukemia (ANLL; also referred to as acute myelogenous leukemia [AML]) in adults for remission induction as first-line therapy or for remission induction in relapsed or refractory patients.[1,2,3,4,5,6,7,8,9,10,11]
- Acute lymphocytic leukemia (ALL) as second-line treatment in adults and children.[12,13,14,15]

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

ZAVEDOS® (Idarubicin hydrochloride), either as the reconstituted solution or the ready to use solution must be administered only by the intravenous (IV) route (see Section **6.6. Special precautions for disposal and other handling**). A slow administration over 5 to 10 minutes via the tubing of a freely running intravenous infusion of 0.9% sodium chloride or 5% dextrose, 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**).

- **ANLL/AML**. In adult ANLL/AML, the recommended intravenous dose schedule is 12 mg/m^2 daily for 3 days in combination with cytarabine. Idarubicin hydrochloride may also be administered as a single agent and in combination, at a dose of 8 mg/m^2 daily for 5 days.[2,3,6,8,11]

- **ALL**. In adult ALL, the recommended single-agent intravenous dose is 12 mg/m^2 daily for 3 days.[13] In children with ALL, the recommended single-agent intravenous dose is 10 mg/m^2 daily for 3 days.[12,14,15]

All of these dosage schedules should, however, take into account the hematological status of the patient and the doses of other cytotoxic drugs when used in combination.

Dose Modifications

Hepatic or Renal Dysfunction. While no specific dose recommendation can be made based on the limited available data in patients with hepatic and/or renal impairment, dose reductions should be considered in patients with bilirubin and/or creatinine serum levels greater than 2.0-mg% (see Section **4.4. Special warnings and precautions for use**).[5,7,10,34]

Idarubicin hydrochloride should not be administered to patients with severe hepatic and/or renal impairment (see Section **4.3. Contraindications**).

4.3. CONTRAINDICATIONS

- hypersensitivity to idarubicin or any other component of the product, other anthracyclines or anthracenediones.
- severe hepatic impairment.
- severe renal impairment.
- severe myocardial insufficiency.[2,3,9,10,11,24]
- recent myocardial infarction.[3,5,8-11,24]
- severe arrhythmias.[3,9,10,11,24]
- persistent myelosuppression.[24]
- previous treatment with maximum cumulative doses of idarubicin hydrochloride and/or other anthracyclines and anthracenediones[25,26] (see Section **4.4. Special warnings and precautions for use**).

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.

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 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.[18,22] 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.[27,28]

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.[24]

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. Available data on patients treated with oral idarubicin hydrochloride total cumulative doses up to 400 mg/m^2 suggest a low probability of cardiotoxicity.[25,26]

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.[29]

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. 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.[76,81,82]

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.[47,48,49,50,51,52,53,54,55,56,77]

It is probable that the toxicity of idarubicin and other anthracyclines or anthracenediones is additive.[57]

Hematologic Toxicity

Idarubicin 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, 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 this 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. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.[24]

Secondary Leukemia

Secondary leukemia, with or without a pre-leukemic phase, has been reported in patients treated with anthracyclines, including idarubicin.[40,41,58,59,77] Secondary leukemia 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 leukemias can have a 1- to 3-year latency period.[30,31,32,33]

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.[15,24,60]

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, 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% (see Section **4.2. Posology and method of administration**).[5,7,10,34]

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. Posology and method of administration**).[35]

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.[61]

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.[36]

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including idarubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving idarubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.[62,63,64,77]

Other

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism have been coincidentally reported with the use of idarubicin.[37,40,41]

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Idarubicin is a potent myelosuppressant and combination chemotherapy regimens that contain other agents with similar action may lead to additive toxicity, especially with regard to bone marrow/hematologic and gastrointestinal effects (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.[43,44,45]

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**).[24,77]

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

4.6. FERTILITY, PREGNANCY AND LACTATION

(See also Section **5.3. Preclinical safety data**).

Impairment of Fertility

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

Pregnancy

The embryotoxic potential of idarubicin has been demonstrated in both *in vitro* and *in vivo* studies. However, there are no adequate and well-controlled studies in pregnant women.

Idarubicin should be used during pregnancy only if 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 to avoid becoming pregnant during treatment. Women of childbearing potential should be advised to use effective contraception during treatment with idarubicin and for at least 6.5 months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with idarubicin and for at least 3.5 months after the last dose.[38,61,77,83]

Lactation

It is not known whether idarubicin or its metabolites are excreted in human milk.[61,77] Mothers should be advised not to breast-feed while undergoing chemotherapy with this drug.

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 following adverse events (not listed in order of frequency) have been reported in association with idarubicin therapy (see also Section **4.4. Special warnings and precautions for use**):

- *Infections and infestations*: infection, sepsis/septicemia
- *Neoplasms benign, malignant and unspecified:* secondary leukemias (acute myeloid leukemia and myelodysplastic syndrome)[40,41,58,59,77]
- *Blood and lymphatic system disorders:* anemia, leukopenia, neutropenia, thrombocytopenia
- *Immune system disorders:* anaphylaxis[41]
- *Metabolism and nutrition disorders:* anorexia, dehydration, hyperuricemia
- *Cardiac disorders:* atrioventricular block, bundle branch block, congestive heart failure, myocarditis, pericarditis, sinus tachycardia, tachyarrhythmias
- *Vascular disorders:* hemorrhage, hot flashes, phlebitis, shock, thrombophlebitis, thromboembolism[40,41]

- *Gastrointestinal disorders:* abdominal pain or burning sensation, colitis (including severe enterocolitis/neutropenic enterocolitis with perforation), diarrhea, erosions/ulceration, esophagitis, gastrointestinal tract bleeding, mucositis/stomatitis, nausea, vomiting
- *Skin and subcutaneous tissue disorders:* acral erythema,[39] alopecia, hypersensitivity of irradiated skin ('radiation recall reaction'), local toxicity,[39,40,41] rash/itch, skin changes, skin and nail hyperpigmentation,[42] urticaria
- *Renal and urinary disorders:* red color to the urine for 1-2 days after administration
- *General disorders and administration site conditions*: fever
- *Investigations:* asymptomatic reductions in left ventricular ejection fraction,[39,40] ECG abnormalities, elevation of liver enzymes and bilirubin.

4.9. OVERDOSE

Very high doses of idarubicin may cause acute myocardial toxicity within 24 hours and severe myelosuppression within 1 to 2 weeks. Delayed cardiac failure has been seen with the anthracyclines up to several months after an overdose.[46]

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Idarubicin is a DNA intercalating analogue of daunorubicin, which has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II. The absence of a methoxy group at 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.[65,66]

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 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,* antitumoral activity in experimental models. In the rat, idarubicinol, administered at the same doses as the parent drug, is clearly less cardiotoxic than idarubicin.[65,66]

5.2. PHARMACOKINETIC PROPERTIES

After IV administration to patients with normal renal and hepatic function, idarubicin is eliminated from systemic circulation with a terminal plasma half-life ranging between 11 and 25 hours and is extensively metabolized to an active metabolite, idarubicinol, which is more slowly eliminated with a plasma half-life ranging between 41 and 69 hours. The drug is eliminated by biliary and renal excretion, mostly in the form of idarubicinol.[65]

Studies of cellular (nucleated blood and bone marrow cells) drug concentrations in leukemic patients have shown that peak cellular idarubicin concentrations are reached a few minutes after injection. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than a hundred times the plasma concentrations. Idarubicin disappearance rates in plasma and cells were

almost comparable with a terminal half-life of about 15 hours. The terminal half-life of idarubicinol in cells was about 72 hours.[65]

Special populations

Hepatic and renal impairment. The pharmacokinetics of idarubicin in patients with hepatic and/or renal impairment have not been fully evaluated. It is expected that in patients with moderate or severe hepatic dysfunction, the metabolism of idarubicin may be impaired and lead to higher systemic drug levels. The disposition of idarubicin may also be affected by renal impairment. Therefore, a dose reduction should be considered in patients with hepatic and/or renal impairment (see Sections **4.2. Posology and method of administration** and **4.4. Special warnings and precautions for use**) and idarubicin is contraindicated in patients with severe hepatic and/or renal failure (see Section **4.3. Contraindication**).[5,7,10,34]

Pediatric. Pharmacokinetic measurements in 7 pediatric patients receiving intravenous idarubicin hydrochloride in doses ranging from 15 to 40 mg/m^2/3 day course of treatment, showed a median idarubicin half-life of 8.5 hours (range: 3.6 – 26.4 hours). The active metabolite, idarubicinol, accumulated during the 3 day therapy, exhibiting a median half-life of 43.7 hours (range: 27.8-131 hours).[78,79]

In a separate study, pharmacokinetic measurements in 15 pediatric patients receiving oral idarubicin hydrochloride in doses ranging from 30 to 50 mg/m^2/3 day course of treatment, showed a median terminal half-life of idarubicin of 9.2 hours (range: 6.4-25.5 hours). Significant accumulation of idarubicinol was seen over the 3 day treatment period.[78,80]

5.3. PRECLINICAL SAFETY DATA

Idarubicin was genotoxic in most of the *in vitro* or *in vivo* tests performed. Intravenous idarubicin was carcinogenic, toxic to the reproductive organs, and embryotoxic and teratogenic in rats. No noteworthy effects on the mothers or offspring were seen in rats given intravenous idarubicin during the peri- and post-natal periods up to the dose of 0.2 mg/kg/day. It is not known whether the compound is excreted in breast milk.[65,66] Intravenous idarubicin, like other anthracyclines and cytotoxic drugs, was carcinogenic in rats. A local safety study in dogs showed that extravasation of the drug causes tissue necrosis.[65,66]

The LD_{50} (mean values) of intravenous idarubicin hydrochloride was 4.4 mg/kg for mice, 2.9 mg/kg for rats and about 1.0 mg/kg for dogs. The main targets after a single dose were the hemolymphopoietic system and, especially in dogs, the gastrointestinal tract.[65,66]

The toxic effects after repeated administration of intravenous idarubicin were investigated in rats and dogs. The main targets of intravenous idarubicin in the above animal species were the hemolymphopoietic system, gastrointestinal tract, kidney, liver, and male and female reproductive organs.[65,66]

Concerning the heart, subacute and cardiotoxicity studies indicated that intravenous idarubicin was slightly to moderately cardiotoxic only at lethal doses while doxorubicin and daunorubicin produced clear myocardial damage at non-lethal doses.[65,66]

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lactose monohydrate.

6.2. 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.[67]

6.3. SHELF LIFE

36 Months.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

20°C to 25°C.

6.5. NATURE AND CONTENTS OF CONTAINER

ZAVEDOS® (Idarubicin HCl) is freeze dried powder for solution for injection available as 5 mg vial and 10 mg vial.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation of the solution

Idarubicin hydrochloride in a 5-, 10-, or 20-mg vial must be dissolved in 5, 10, and 20 mL respectively of Water for Injections only. The resulting solution is hypotonic and the recommended administration procedure described below must be followed.

Protective measures[68,69,70,71,72,73,74,75]

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

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling idarubicin should wear protective clothing: goggles, gowns, and disposable gloves and masks.
- 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.
- Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution, medical attention should be sought.

- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.
- Discard any unused solution.

Zavedos/LPD/PK-04
According to CDS V 06 dated: 06 August, 2020; Supersedes CDS V 05 dated: 21 November, 2018

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