

AUSTRALIAN PRODUCT INFORMATION – ZAVEDOS® (idarubicin hydrochloride)

1. NAME OF THE MEDICINE

Idarubicin hydrochloride.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder for Injection

Each vial contains 5 mg, 10 mg or 20 mg of idarubicin hydrochloride.

Solution for Injection

Each vial contains 5 mg/5 mL, 10 mg/10 mL or 20 mg/20 mL of idarubicin hydrochloride.

Capsules

Each capsule contains 5 mg or 25 mg of idarubicin hydrochloride.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for Injection

Porous, red-orange freeze dried powder, cake or mass..

The reconstituted solution is an orange-red, mobile solution, free from particles.

Solution for injection

Red-orange, clear, mobile solution, free from particles.

Capsules

The 5 mg capsules is a hard gelatin capsule, self-locking, with opaque red-orange cap & body, size No.4, with a radial imprint on the cap "idarubicin 5" with black ink. The capsules contain an orange powder.

The 25 mg capsules is a hard gelatin capsule, self-locking, with opaque white cap and body, size No.2, with a radial imprint on the cap "idarubicin 25" with black ink. The capsules contain an orange powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZAVEDOS is indicated for use in acute myelogenous leukaemia (AML) in adults for remission induction in untreated patients or for remission induction in relapsed or refractory patients. ZAVEDOS capsules are indicated whenever the intravenous route is not considered suitable. ZAVEDOS may be used in combination chemotherapy regimens involving other cytotoxic agents.

4.2 Dose and Method of Administration

Dose

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

Capsules

In adult AML the recommended dose schedule is 30 mg/m² orally given daily for 3 days as a single agent, or between 15 and 30 mg/m² orally daily for three days in combination with other antileukaemic agents. These dosage schedules should, however, take into account the haematological status of the patients and the dosages of other cytotoxic drugs when used in combination. In patients with hepatic or renal impairment a dose reduction of ZAVEDOS should be considered (see Section 4.4 Special warnings and precautions for use).

Before administration, it should be ensured that the capsules are intact. They should be swallowed whole with some water and should not be sucked, bitten or chewed. ZAVEDOS capsules may also be taken with a light meal.

In case of accidental contact of the powder for the capsules with the eye, skin or mucosa, the area should be immediately and thoroughly rinsed with water: medical attention should be sought.

Powder for Injection and Solution for Injection

ZAVEDOS 12 mg/m² daily for three days by slow (10-15 min) intravenous injection in combination with Ara-C, 100 mg/m² daily given by continuous infusion for seven days. In patients with unequivocal evidence of leukaemia after the first induction course, a second course may be administered. Administration of the second course should be delayed in patients who experienced severe mucositis, until recovery from this toxicity has occurred, and a dose reduction of 25% is recommended.

Powder for Injection

ZAVEDOS 5 mg, 10 mg and 20 mg powder for injection vials should be reconstituted with 5 mL, 10 mL and 20 mL, respectively, of Water for Injections only to give a final concentration of 1 mg/mL of idarubicin hydrochloride. Bacteriostatic diluents are not recommended.

The vial contents are under a negative pressure to minimise aerosol formation during reconstitution therefore particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided.

Reconstituted solutions are physically and chemically stable for at least 48 hours under refrigeration (2°C to 8°C) and 24 hours at room temperature. To reduce microbiological hazard, use as soon as practical after reconstitution/preparation. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours. The reconstituted solutions do not contain an antimicrobial preservative. Use in one patient on one occasion only. Discard any residue.

Note: The reconstituted and diluted solution is light sensitive. Therefore, after preparation, protect from light. Also see Section 6.4 Special precautions for storage.

Dosage Adjustment

Hepatic and Renal Impairment

ZAVEDOS should not be administered in patients with severe renal and liver impairment (see Section 4.3 - Contraindications). Dose adjustment should be considered in patients with moderate liver and renal impairment (refer to Sections 5.2 Pharmacokinetic properties and 4.4 Special warnings and precautions for use). With anthracyclines a 50% dose reduction is generally employed if bilirubin levels are in the range 20.4-51.0 micromoles/ litre.

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

Method of Administration

Capsules

Oral administration.

Powder for Injection and Solution for Injection

Intravenous infusion.

ZAVEDOS powder for injection and ZAVEDOS solution for injection do not contain antimicrobial preservative. Use in one patient on one occasion only. Discard any residue.

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

The tubing should be attached to a butterfly needle or other suitable device and inserted preferably into a large vein. This technique minimises the risk of thrombosis or perivenous extravasation, which can lead to severe cellulitis and necrosis. Venous sclerosis may result from injection into small veins or repeated injections in the same vein.

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

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

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

Instructions for Use and Handling and Disposal

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

- Personnel should be trained in good technique for 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.

4.3 Contraindications

ZAVEDOS therapy is contraindicated in patients with severe renal and liver impairment or patients with uncontrolled infections. It should also not be administered to individuals with hypersensitivity to idarubicin or any other component of the product (see Section 6.1 List of excipients) and/or other anthracyclines.

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

ZAVEDOS therapy is contraindicated in pregnant women or women wishing to become pregnant (see Section 4.6 Fertility, pregnancy and lactation , Use in pregnancy).

4.4 Special warnings and precautions for use

General

ZAVEDOS is intended for use under the direction of those experienced in leukaemia chemotherapy. Close monitoring for toxicity is mandatory. The drug should not be given to

patients with pre-existing bone marrow depression induced by previous drug therapy or radiotherapy unless the benefit warrants the risk.

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

Pre-existing heart disease and previous therapy with anthracyclines, especially at high cumulative doses, or other potentially cardiotoxic agents are co-factors for increased risk of idarubicin-induced cardiac toxicity: the benefit to risk ratio of idarubicin therapy in such patients should be weighed before starting treatment with ZAVEDOS. In absence of sufficient data, the use of oral idarubicin is not recommended in patients with prior total body irradiation or bone marrow transplantation. Like most other cytotoxic agents, idarubicin has mutagenic properties and is carcinogenic in rats.

Haematologic Toxicity

ZAVEDOS is a potent bone marrow suppressant. Myelosuppression, primarily of 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.

Secondary Leukaemia

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

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

Myocardial toxicity as manifested by potentially fatal congestive heart failure, acute life threatening arrhythmias or other cardiomyopathies, may occur during therapy or several weeks after termination of therapy.

Idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative IV doses of 150 to 290 mg/m². Although cumulative dose limits are yet to be defined, available data on patients treated with ZAVEDOS capsules indicate that total cumulative doses up to at least 400 mg/m² have a low probability of cardiotoxicity. Should CHF occur, treatment with digitalis, diuretics, sodium restriction and bed-rest is indicated.

Cardiac Function

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

Early (Acute) Events. Early cardiotoxicity of idarubicin consists mainly of sinus tachycardia and/or ECG abnormalities, such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well

as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity.

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

Cardiac function should be monitored carefully during treatment in order to minimise the risk of cardiac toxicity of the type described for other anthracycline compounds. Risk factors for cardiac toxicity include concomitant or previous radiation to the mediastinal/pericardial area, previous treatment with other anthracyclines or anthracenediones at high cumulative doses, and concomitant use of drugs with the ability to suppress cardiac contractility or other potentially cardiotoxic agents (e.g., trastuzumab). Anthracyclines including idarubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see Section 4.5 Interactions with other medicines and other forms of interactions). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab (variable half-life; washout period up to 7 months), may also be at an increased risk of developing cardiotoxicity.

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

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

While there is no reliable method for predicting acute congestive heart failure, cardiomyopathy induced by anthracyclines is usually associated with persistent QRS voltage reduction, increase beyond normal limits of the systolic time interval (PEP/LET) and decrease of the left ventricular ejection fraction (LVEF) from pre-treatment baseline values.

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

Severe enterocolitis with perforation has been reported rarely. The risk of perforation may be increased by instrumental intervention. The possibility of perforation should be considered in

patients who develop severe abdominal pain and appropriate steps for diagnosis and management should be taken.

Use in Hepatic Impairment

Since impairment of hepatic function may affect the disposition of idarubicin, liver function should be evaluated with conventional clinical laboratory tests (using serum bilirubin) prior to and during treatment. Idarubicin is contraindicated in severe hepatic impairment. Also refer to Sections 4.2 Dose and method of administration.

Use in Renal Impairment

Since impairment of renal function may affect the disposition of idarubicin, kidney function should be evaluated with conventional clinical laboratory tests (using serum creatinine as indicators) prior to and during treatment. Idarubicin is contraindicated in severe renal impairment. Also refer to Sections 4.2 Dose and method of administration.

Tumour Lysis Syndrome

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

Effects at Site of Injection

With intravenous administered ZAVEDOS, extravasation at the site of injection can cause severe local tissue necrosis. Extravasation may occur with or without accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If signs or symptoms of extravasation occur, the injection or infusion should be terminated immediately and restarted in another vein (see Section 4.2 Dose and method of administration).

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

Immunosuppressant Effects/Increased Susceptibility to Infections

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

Other

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

Use in the Elderly

No data available.

Paediatric Use

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.

Effects on Laboratory Tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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

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

Food does not appear to reduce idarubicin absorption; therefore, ZAVEDOS capsules may be given with a light meal.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

No data available.

Use in Pregnancy - Category D

There is no information as to whether idarubicin adversely affects fertility or causes teratogenesis in humans. However, it is teratogenic and embryotoxic in rats at intravenous doses of 0.7-1.4 mg/m²/day. In rabbits, no evidence of teratogenicity was seen at the highest dose tested (2.2 mg/m²/day, or one fifth of the human intravenous dose), which caused some maternal deaths. ZAVEDOS should not be used during pregnancy (see Section 4.3 Contraindications), and women of child bearing potential should be advised to avoid pregnancy. If the patient becomes pregnant during therapy, the patient should be informed of the potential hazard to the foetus.

Given the mutagenic potential of idarubicin, the drug could induce chromosomal damage in human spermatozoa; for this reason, males undergoing idarubicin treatment should use contraceptive measures.

Use in Lactation

It is not known whether idarubicin or its metabolites are excreted in human milk. Mothers should be advised not to breast feed while undergoing chemotherapy with ZAVEDOS.

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. Special care should be taken if it is essential that patients drive or operate machinery while undergoing treatment with ZAVEDOS, especially if in a debilitated condition.

4.8 Adverse effects (undesirable effects)

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

Adverse reactions that occur more frequently than 1% include:

General: Fever, infection.

Blood: Bone marrow depression.

Circulation: Cardiomyopathy, ECG changes.

Gastrointestinal: Acute nausea and vomiting, stomatitis, oesophagitis, diarrhoea.

Skin: Alopecia, skin rash.

Liver: Bilirubin and liver enzyme elevation.

Myelosuppression

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

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

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

Gastrointestinal

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

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

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

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.

Anorexia, burning sensation, erosions/ulceration, gastrointestinal tract bleeding and colitis have also been reported.

Dermatological

Alopecia is reported frequently and dermatological reactions including rash/itch, urticaria and a bullous erythrodermatous rash of the palms and soles can occur. The dermatological reactions are usually attributable to concomitant antibiotic therapy, skin changes, skin and nail hyperpigmentation, hypersensitivity of irradiated skin ('radiation recall reaction'), acral erythema, local toxicity (see Section 4.4 Special warnings and precautions for use) and local reactions including hives at the injection site have been reported.

Hepatic and Renal

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

Idarubicin may impart a red colour to the urine for 1-2 days after administration and patients should be advised that this is no cause for alarm.

Cardiac

As in the case of other anthracyclines, cardiac toxicity, as manifested by congestive heart failure (frequently attributed to fluid overload), serious life-threatening arrhythmias including atrial fibrillation, chest pain, myocardial infarction and asymptomatic declines in LVEF, have been reported in patients undergoing induction therapy for AML (see Section 4.4 Special warnings and precautions for use). Myocardial insufficiency and arrhythmias are usually reversible and occur in the setting of sepsis, anaemia and aggressive intravenous fluid administration. The events were reported more frequently in patients over age 60 years and in those with pre-existing cardiac disease. Serious cardiac impairment may be prevented through regular surveillance during the course of treatment (see Section 4.4 Special warnings and precautions for use). Subacute effects such as pericarditis/myocarditis have also been reported.

Sinus tachycardia, tachyarrhythmias, atrio-ventricular and bundle branch block have also been reported.

Endocrine

Vasomotor instability (hot flushes) have been reported.

Vascular

Phlebitis, thrombophlebitis and thromboembolism have been reported.

Other

Anaphylaxis, sepsis/septicaemia, secondary leukaemias (acute myeloid leukemia and myelodysplastic syndrome), shock, fever, chills and hyperuricaemia have been reported.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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, as overdose may result in increased severity of gastrointestinal toxicity.

Two cases of fatal overdosage in patients receiving therapy for AML have been reported. The doses were 135 mg/m² over 3 days, and 45 mg/m² of idarubicin and 90 mg/m² of daunorubicin over a 3-day period.

There is no known antidote to ZAVEDOS. Treatment should aim to support the patient and should utilise such measures as blood transfusions, reverse-barrier nursing, antibiotics and symptomatic treatment of mucositis. Patients should be observed carefully and if signs of cardiac failure arise, should be treated along conventional lines.

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

The single-dose packing of ZAVEDOS capsules is designed to minimise the risk of overdosage.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ZAVEDOS is a semi synthetic antineoplastic anthracycline for intravenous or oral use.

Mechanism of Action

Idarubicin is a cytotoxic agent. It is a DNA intercalating agent which reacts with topoisomerase II and has an inhibitory effect on nucleic acid synthesis. The compound has a high lipophilicity

which results in an increased rate of cellular uptake compared with doxorubicin and daunorubicin.

Pharmacodynamic Effects

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

Clinical Trials

No data available.

5.2 Pharmacokinetic properties

Intravenous

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

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

Peak cellular idarubicin concentrations are reached a few minutes after injection. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than a hundred times the plasma concentrations. Idarubicin elimination half-life in cells is about 15 hours and is similar to that in plasma. The elimination half-life for idarubicinol in cells is 72 hours.

Excretion takes place via the liver and kidneys, mainly in the form of idarubicinol. After intravenous administration of 13 mg/m² ¹⁴C-idarubicin, 33% of the dose was excreted in urine and 39% in faeces after 14 days. Idarubicin excreted unchanged in urine accounts for 2-7% of the dose, and idarubicinol, 9-13%. In a patient with percutaneous biliary drainage, 17% of the dose was eliminated through the bile (as idarubicin plus idarubicinol) over five days.

Oral

After oral administration to patients with normal renal and hepatic function, idarubicin is rapidly absorbed, reaching maximum concentrations between 2-4 hours post dose. Idarubicin is eliminated from the systemic circulation with an elimination plasma $t_{1/2}$ ranging between 10-35 hours and is extensively metabolized to an active metabolite, idarubicinol, which is more slowly eliminated with a plasma $t_{1/2}$ ranging between 33 and 60 hours. After oral administration of 46 mg/m² ¹⁴C-idarubicin, 30% of the dose was excreted in urine and 61% in faeces after 14 days. Idarubicin excreted unchanged in urine accounts for 1-2% of the dose,

and idarubicinol, 5%. In a patient with percutaneous biliary drainage, 8% of the dose was eliminated through the bile (as idarubicin plus idarubicinol) over five days.

The absolute bioavailability of idarubicin has been shown to range between 18 and 39%, whereas that calculated from the data on the active metabolite, idarubicinol, is somewhat higher (29-58%). The effective bioavailability, calculated on the basis of the pharmacological response, is approximately 35%.

Studies on cellular (nucleated blood and bone marrow cells) drug concentrations in leukaemic patients have shown that uptake is rapid and most parallels the appearance of the drug in plasma. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than two hundred times the plasma concentrations. Idarubicin and idarubicinol disappearance rates in plasma and cells were almost comparable.

Special Populations

Renal impairment

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

Hepatic impairment

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

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Long-term carcinogenicity studies have not been conducted with idarubicin, but like most other cytotoxic agents, idarubicin has mutagenic properties and is carcinogenic in rats. In male dogs, testicular atrophy with inhibition of spermatogenesis and sperm maturation was observed at threshold idarubicin doses 1.8 mg/m² administered intravenously or 3 mg/m² administered orally (3 days/week for 13 weeks). These effects were not readily reversible after an eight week recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for Injection

Lactose monohydrate.

Solution for Injection

Glycerol

Hydrochloric acid for adjustment to pH 3.5

Water for injections.

Capsules

5mg and 25 mg

Gelatin

Glyceryl palmitostearate

Microcrystalline cellulose

TekPrint SW-9008 Black Ink

Titanium dioxide.

The 5 mg capsules also contain red iron oxide.

6.2 Incompatibilities

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

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Powder for Injection

Store below 25°C. Protect from light.

After reconstitution of ZAVEDOS powder for injection, protect from light.

Reconstituted solutions are physically and chemically stable for at least 48 hours under refrigeration (2°C to 8°C) and 24 hours at room temperature. To reduce microbiological hazard, use as soon as practical after reconstitution/preparation. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

The reconstituted solutions do not contain an antimicrobial preservative. Use in one patient on one occasion only. Discard any residue.

Solution for Injection

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

Capsules

Store below 25°C.

6.5 Nature and contents of container

ZAVEDOS powder for injection is supplied in single use only, glass vials.

ZAVEDOS solution for injection is supplied in single use only, polypropylene vials.

ZAVEDOS capsules are supplied in amber glass bottles containing one capsule.

Not all presentations may be marketed.

6.6 Special precautions for disposal

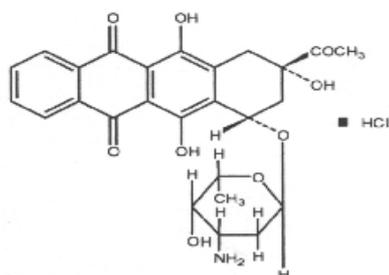
All items used for reconstitution, administration or cleaning, including gloves should be placed in high-risk, waste-disposal bags for high temperature incineration.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

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

Chemical structure



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

CAS number

57852-57-0.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000.

Toll Free Number: 1800 675 229.
www.pfizer.com.au.

9. DATE OF FIRST APPROVAL

Powder for injection

5 mg/5 mL: 19 August 1991.

10 mg/10 mL: 06 December 1993.

20 mg/20 mL: 16 February 1995.

Solution for injection

5mg,10mg and 20mg: 19 August 1999.

Capsules

5 mg and 25 mg: 25 October 2000.

10. DATE OF REVISION

20 February 2020.

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2, 3, 4 and 6	Minor editorial changes to align with new PI format.
4.4	Update to half-life of trastuzumab emtansine.
8	Sponsor details updated