NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ZAVEDOS® 5 mg, 10 mg Powder for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of ZAVEDOS Powder for Injection contains 5 mg or 10 mg of idarubicin hydrochloride.

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

3. PHARMACEUTICAL FORM

Powder for Injection.

ZAVEDOS 5 mg and 10 mg Powder for Injection is a sterile, orange-red lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZAVEDOS is an antimitotic and cytotoxic agent. It 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 is also an effective agent for use in the second line treatment of advanced breast cancer either as a single agent or in a combination regimen.

4.2 Dose and method of administration

ZAVEDOS treatment should be initiated or overseen by personnel experienced in chemotherapy. Dosage is usually calculated on the basis of body surface area.

Dose

For induction therapy in adult patients with AML, the following dose schedule is recommended:

ZAVEDOS 12 mg/m^2 daily for 3 days by slow (10-15 min) intravenous injection in combination with cytarabine 100 mg/m^2 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.

For reconstitution of the freeze-dried formulation, see Method of administration below. Also refer to Section 6.4 Special precautions for storage for storage conditions for the unreconstituted Powder for injection and the reconstituted solution.

Food does not appear to reduce absorption and ZAVEDOS may therefore, be given with a light meal. All dosage schedules should take into account the haematological status of the patient and the dosages of the other cytotoxic drugs when used in combination.

Dose adjustments

Hepatic or Renal impairment

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/dL (see Section 4.4 Special warnings and precautions for use).

ZAVEDOS should not be administered in patients with severe hepatic and renal impairment (see Section 4.3 Contraindications).

Special populations

Paediatric population

See Section 4.4 Special warnings and precautions for use, Paediatric population.

Method of administration

The reconstituted solution of ZAVEDOS must be administered only by the intravenous route.

Preparation of the solution

ZAVEDOS 5 mg vial and 10 mg vial must be dissolved in 5 and 10 mL respectively of Water for Injections only. The resulting solution is hypotonic and the recommended administration procedure via a freely running intravenous infusion must be followed.

A slow administration (over 10 to 15 minutes) via the tubing of a freely running intravenous infusion of 0.9% sodium chloride, must be followed. 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 into the same vein. 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, Effect at site of injection and Extravasation).

Protective measures

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 idarubicin.
- 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.

Care should be taken to prevent inhaling particles and exposing the skin to idarubicin.

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 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.

Seek immediate medical attention if the drug is ingested or inhaled.

ZAVEDOS contains no antimicrobial preservative. Use in one patient on one occasion only. Discard any residue.

4.3 Contraindications

ZAVEDOS is contraindicated in patients with:

- hypersensitivity to idarubicin or any other component of the product, other anthracyclines or anthracenediones
- severe hepatic impairment
- severe renal impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- persistent myelosuppression previous treatment with maximum cumulative doses of idarubicin and/or other anthracyclines and anthracenediones.

ZAVEDOS is contraindicated in pregnant women or women wishing to become pregnant. See also Section 4.6 Fertility, Pregnancy and lactation, Use in Pregnancy.

4.4 Special warnings and precautions for use

General

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

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 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 (delayed) events

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

Cumulative dose limits for intravenous or oral idarubicin have not been defined. However, idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative intravenous 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 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, 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.

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

In infants and children there appears to be a greater susceptibility to anthracycline-induced cardiac toxicity, and a long-term periodic evaluation of cardiac function has to be performed.

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

Haematologic toxicity

ZAVEDOS is a potent bone marrow suppressant. Severe myelosuppression will occur in all patients given a therapeutic dose of this agent. Haematologic profiles should be assessed before and during each cycle of therapy with idarubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of idarubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia and neutropenia are usually severe; thrombocytopenia and anaemia may also occur. Neutrophil and platelet counts usually reach their nadir 10 to 14 days following administration; however, cell counts generally return to normal levels during the third week. Clinical consequences of severe myelosuppression may include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

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.

Gastrointestinal

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

Occasionally, episodes of serious gastrointestinal events (such as perforation or bleeding) have been observed in patients receiving oral idarubicin who had acute leukaemia or a history of other pathologies or had received medications known to lead to gastrointestinal complications. The possibility of perforation should be considered in patients who develop severe abdominal pain and appropriate steps for diagnosis and management should be taken.

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 minimise the risk of phlebitis/thrombophlebitis at the injection site (see Sections 4.2 Dose and method of administration and 6.4Special precautions for storage).

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.

Tumour lysis syndrome

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

Immunosuppressant effects/increased susceptibility to infection

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

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

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.

Use in patients with hepatic and/or renal impairment

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/dL. With other anthracyclines a 50% dose reduction is generally used if bilirubin levels are in the range 1.2 to 2.0 mg/dL (see Section 4.2 Dose and method of administration).

Paediatric population

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.

4.5 Interaction with other medicines and other forms of interaction

ZAVEDOS 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/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 (e.g., hepatotoxic and nephrotoxic antibiotics and antifungal agents) 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.

4.6 Fertility, pregnancy and lactation

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 - Category D

Idarubicin should not be used during pregnancy (see Section 4.3 Contraindications). The embryotoxic potential of idarubicin has been demonstrated in both *in vitro* and *in vivo* studies. In rats (but not rabbits) it is teratogenic and embryotoxic. 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.

Lactation

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

4.7 Effects on ability to drive and use machinery

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 especially in a debilitated condition.

4.8 Undesirable effects

Severe myelosuppression and cardiac toxicity are the two major adverse effects. Other adverse reactions include reversible alopecia in most patients; acute nausea and vomiting; mucositis; diarrhoea; fever and chills; skin rash; elevation of liver enzymes and bilirubin in about 10-20% of cases. Severe and sometimes fatal infections have been associated with idarubicin alone or in combination. Severe enterocolitis with perforation has been reported very rarely.

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

Infections, sepsis/septicaemia.

Neoplasms benign, malignant and unspecified

Secondary leukaemias (acute myeloid leukaemia and myelodysplastic syndrome).

Blood and lymphatic system disorders

Anaemia, leukopenia, neutropenia, thrombocytopenia.

Immune system disorders

Anaphylaxis.

Metabolism and nutrition disorders

Anorexia, dehydration, hyperuricaemia.

Cardiac disorders

Atrioventricular block, bundle branch block, congestive heart failure, myocarditis, pericarditis, sinus tachycardia, tachyarrhythmias.

Vascular disorders

Haemorrhage, hot flushes, phlebitis, shock, thrombophlebitis, thromboembolism.

Gastrointestinal disorders

Abdominal pain or burning sensation, colitis (including severe enterocolitis/neutropenic enterocolitis with perforation), diarrhoea, erosions/ulceration, oesophagitis, gastrointestinal tract bleeding, mucositis/stomatitis, nausea, vomiting.

Skin and subcutaneous tissue disorders

Acral erythema, alopecia, hypersensitivity of irradiated skin ('radiation recall reaction'), local toxicity, rash/itch, skin changes, skin and nail hyperpigmentation, urticaria, bullous erythrodermatous rash of the palm and soles.

Renal and urinary disorders

Red colour to the urine for 1-2 days after administration.

General disorders and administration site conditions

Fever.

Investigations

Asymptomatic reductions in left ventricular ejection fraction, ECG abnormalities, elevation of liver enzymes and bilirubin.

Description of selected adverse events.

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 or death. Intravenous antibiotics should be given in the presence of febrile neutropenia.

Gastrointestinal disorders

Nausea and/or vomiting, mucositis (usually involving the oral mucosa and appearing 3-10 days after starting treatment), abdominal pain or burning sensation, 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.

Skin and subcutaneous tissue disorders

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.

Cardiac disorders

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

The single dose packaging is designed to minimise the risk of overdosage and no data on oral overdosage exists. Patients treated with oral idarubicin should be observed for possible gastrointestinal haemorrhage and severe mucosal damage.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Idarubicin is an anti-mitotic and cytotoxic agent which intercalates with DNA and interacts with topoisomerase II and has an inhibitory effect on nucleic acid synthesis.

The modification in 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.

Pharmacodynamic effects

ZAVEDOS 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 *in vitro* and *in vivo*, antitumoural activity in experimental models. In the rat, idarubicinol, administered at the same doses as the parent drug, is clearly less cardiotoxic than idarubicin.

5.2 Pharmacokinetic properties

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/m^2 ^{14}C-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.

After oral administration to patients with normal hepatic and renal function, idarubicin is rapidly absorbed, with a peak time of 2-4 hours, is eliminated from systemic circulation with a terminal plasma $t_{1/2}$ ranging between 10-35 hours and is extensively metabolised 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/m^2 ^{14}C-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 on the data from the active metabolite, idarubicinol, is somewhat higher (29-58%). The effective bioavailability calculated on the basis of pharmacological response is approximately 35%.

Studies of 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 with a terminal half-life of about 15 hours. The terminal half-life of idarubicinol in cells was about 72 hours.

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

Idarubicin was genotoxic in most of the *in vitro* or *in vivo* tests performed.

Carcinogenicity

Intravenous idarubicin was carcinogenic, toxic to the reproductive organs, and embryotoxic and teratogenic in rats. However, 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. Idarubicin can induce chromosomal damage in human spermatozoa. For this reason, males undergoing idarubicin treatment should use contraceptive methods.

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. ZAVEDOS should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Unreconstituted Powder for Injection

Store at or below 25°C.

Reconstituted solution

Idarubicin lyophilised powder must be reconstituted with Water for Injections. The solution obtained is stable for at least 48 hours under refrigeration (2°C to 8°C) and 24 hours at room temperature (20°C to 25°C). However, in order to avoid the risk of microbial contamination, it is recommended that the solution be used as soon as possible after reconstitution.

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

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and containers permit.

6.5 Nature and contents of container

ZAVEDOS 5 mg and 10 mg Powder for Injection is supplied as a single use only vial.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand.

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

05 November 1992.

10. DATE OF REVISION OF THE TEXT

01 December 2020.

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Summary table of changes

Section changed	Summary of new information
All	Minor editorial changes to remove reference to capsules and Zavedos 20 mg powder for injection, which are not supplied in NZ.
4.6	Inclusion of contraception information and fertility preservation for both males and females.