SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ZAVEDOS® 5 mg Powder for solution for injection

ZAVEDOS® 10 mg Powder for solution for injection

ZAVEDOS® RTU 5 Solution for injection

ZAVEDOS® RTU 10 Solution for injection

ZAVEDOS® RTU 20 Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZAVEDOS Powder for solution for injection

Each vial of ZAVEDOS 5 mg and ZAVEDOS 10 mg contains 5 mg and 10 mg idarubicin hydrochloride respectively.

Contains sugar (lactose monohydrate).

Excipients with known effect

ZAVEDOS 5 mg powder for solution for injection contains 53,7 mg lactose monohydrate per vial.

ZAVEDOS 10 mg powder for solution for injection contains 107,4 mg lactose monohydrate per vial.

ZAVEDOS RTU Solution for injection

Each vial of ZAVEDOS RTU 5, ZAVEDOS RTU 10 and ZAVEDOS RTU 20 contains 5 mg, 10 mg and 20 mg idarubicin hydrochloride respectively.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ZAVEDOS Powder for solution for injection

Porous red-orange, freeze-dried cake or mass in a clear glass vial.

ZAVEDOS RTU Solution for injection

Plastic vials containing a red-orange, clear mobile solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute non-lymphocytic leukaemia (ANLL), including acute myeloblastic leukaemia (AML) in adults, for remission induction as front-line therapy, or for remission induction in relapsed or refractory patients.

ZAVEDOS, in combination with cytarabine, is indicated for the first remission induction-line treatment of previously untreated children with acute myeloid leukaemia (AML).

4.2 Posology and method of administration

Posology

Acute non-lymphocytic leukaemia (ANLL) or acute myeloblastic leukaemia (AML)

In adults the suggested dose schedule is 12 mg/m^2 body surface area IV daily for 3 days in combination with cytarabine. Alternatively, a dose of 8 mg/m^2 IV may be given daily for 5 days.

In children with AML the recommended dose range of ZAVEDOS, in combination with cytarabine, is 10 - 12 mg/m^2 body surface daily for 3 days by slow IV injection.

All dose schedules should, however, take into account the haematological status of the patient and the dosage of other cytotoxic medicine when used in combination.

Special populations

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/dL (bilirubin > 34,2 µmol/L and/or serum creatinine > 176,8 µmol/L) (see section 4.4).

ZAVEDOS should not be administered to patients with severe hepatic and/or renal impairment (see section 4.3).

Method of administration

Intravenous administration

ZAVEDOS, either as the reconstituted solution or the ready-to-use (RTU) solution, must ONLY be administered via the intravenous (IV) route.

Slow administration over 5 to 10 minutes via the tubing of a freely running intravenous infusion of 0,9 % sodium chloride must be followed.

A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see section 4.4).

To avoid the risk of microbial contamination, the solution should be used as soon as possible after adding it to the 0,9 % sodium chloride infusion bag.

4.3 Contraindications

- Hypersensitivity to idarubicin or to any of the excipients of ZAVEDOS (listed in section 6.1), and/or other anthracyclines or anthracenediones
- Severe hepatic impairment, including bilirubin levels exceeding 5 mg/dL (85,5 µmol/L)
- Severe renal impairment (CrCL < 30 mL/min)
- Severe myocardial insufficiency (NYHA grade 3 and above)
- Recent myocardial infarction
- Severe dysrhythmias
- Persistent myelosuppression
- Previous treatment with maximum cumulative doses of ZAVEDOS and/or other anthracyclines and anthracenediones (see section 4.4)
- Patients with uncontrolled infections
- Pre-existing bone marrow suppression induced by previous medicine therapy or radiotherapy
- Concomitant use with live attenuated vaccines and yellow fever vaccine
- Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

General

ZAVEDOS IS INTENDED FOR ADMINISTRATION ONLY BY THOSE EXPERIENCED IN THE USE OF CYTOSTATICS.

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

Cardiac function

Cardiotoxicity is a risk of anthracycline treatment, as in ZAVEDOS, that may manifest as early (i.e., acute) or late (i.e., delayed) events. Cardiotoxicity is related to the cumulative dose of anthracycline.

Early (acute) events:

Early cardiotoxicity of ZAVEDOS consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities, such as non-specific ST-T wave changes. Tachydysrhythmias, 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 ZAVEDOS 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 medicine.

Cumulative dose limits for IV ZAVEDOS have not been identified. However, ZAVEDOS related cardiomyopathy was reported in 5 % of patients who received cumulative IV doses of 150 to 290 mg/m^2.

Cardiac function should be assessed before patients undergo treatment with ZAVEDOS and must be monitored throughout therapy to minimise 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 ZAVEDOS 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
- concomitant use of medicines with the ability to suppress cardiac contractility or cardiotoxic medicines (e.g. trastuzumab)

ZAVEDOS should not be administered in combination with other cardiotoxic medicines unless the patient's cardiac function is closely monitored (see section 4.5).

Patients receiving ZAVEDOS after stopping treatment with other cardiotoxic medicines, 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 medical practitioners should avoid ZAVEDOS therapy for up to 7 months after stopping trastuzumab when possible. If ZAVEDOS is 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 ZAVEDOS 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 ZAVEDOS 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 ZAVEDOS. Haematologic profiles should be assessed before and during each cycle of therapy with ZAVEDOS, including differential white blood cell (WBC) counts.

A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of ZAVEDOS haematologic toxicity and is the most common acute dose-limiting toxicity of this medicine. Leukopenia and neutropenia are usually severe; thrombocytopenia and anaemia may also occur. Neutrophil and platelet counts usually reach their nadir 10 to 14 days after administration of ZAVEDOS. Cell counts generally return to normal levels during the third week. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Secondary leukaemia

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

Gastrointestinal

ZAVEDOS is emetogenic. Mucositis (mainly stomatitis, less often oesophagitis) generally appears early after ZAVEDOS 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.

Hepatic and/or renal function

Since hepatic and/or renal function impairment can affect the disposition of ZAVEDOS, 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 withheld if bilirubin and/or creatinine serum levels exceeded 2,0 mg/dL (bilirubin > 34,2 µmol/L and/or serum creatinine > 176,8 µmol/L). With other anthracyclines a 50 % dose reduction is generally used if bilirubin levels are in the range 1,2 to 2,0 mg/dL (20,5 to 34,2 µmol/L) (see section 4.2).

Effects at the 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 section 4.2).

Extravasation

Extravasation of ZAVEDOS 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 ZAVEDOS, the infusion should be stopped immediately.

Tumour lysis syndrome

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

Immunosuppressant effects/increased susceptibility to infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicines including ZAVEDOS may result in serious or fatal infections. Vaccinations with a live vaccine should be avoided in patients receiving ZAVEDOS. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished (see section 4.3).

Other

Thrombophlebitis and thromboembolic phenomena, including pulmonary embolism have been reported with the use of ZAVEDOS.

Lactose

ZAVEDOS 5 mg and ZAVEDOS 10 mg Powder for solution for injection contains lactose. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, the Lapp total lactase deficiency or glucose-galactose malabsorption should not receive ZAVEDOS 5 mg and ZAVEDOS 10 mg Powder for solution for injection.

4.5 Interaction with other medicines and other forms of interaction

ZAVEDOS is a potent myelosuppressant and combination chemotherapy regimens that contain other medicines with similar action may lead to additive toxicity, especially with regard to bone marrow/haematologic and gastrointestinal effects (see section 4.4). The use of ZAVEDOS in combination chemotherapy with other potentially cardiotoxic medicines, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Changes in hepatic or renal function induced by concomitant therapies may affect ZAVEDOS metabolism, pharmacokinetics, and therapeutic efficacy and/or toxicity.

An additive myelosuppressant effect may occur when radiotherapy is given concomitantly or within 2 - 3 weeks

prior to treatment with ZAVEDOS.

4.6 Fertility, pregnancy and lactation

ZAVEDOS is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

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

Women of child-bearing potential should avoid becoming pregnant during treatment (see section 4.3).

The patient should be informed of the potential hazard to the foetus.

Highly effective contraceptives should be used.

Breastfeeding

It is not known whether ZAVEDOS or its metabolites are excreted in human breast milk. Mothers should not breastfeed while undergoing chemotherapy with ZAVEDOS (see section 4.3).

Fertility

ZAVEDOS can induce chromosomal damage in human spermatozoa. For this reason, males undergoing treatment with ZAVEDOS should use effective contraceptive methods during and up to 3 months after treatment.

Males intending to father children should be counselled regarding prior preservation of sperm.

4.7 Effects on ability to drive and use machines

The effect of ZAVEDOS on the ability to drive or use machinery has not been systematically evaluated. Patients

should be made aware that ZAVEDOS may affect their ability to drive or use machinery and it should be determined how they are affected before attempting to do so.

4.8 Undesirable effects

The following adverse events have been reported in association with ZAVEDOS therapy with the following frequencies: very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1 000 to < 1/100; rare ≥ 1/10 000 to < 1/1 000; very rare < 1/10 000, including isolated reports.

System organ class	Frequency	Side effect
Infections and infestations	Very common	Infection, severe and sometimes fatal
	Uncommon	Sepsis/septicaemia
Neoplasms benign, malignant and unspecified	Uncommon	Secondary leukaemias (acute myeloid leukaemia and myelodysplastic syndrome)
Blood and lymphatic system disorders	Very common	Anaemia, leukopenia, neutropenia, thrombocytopenia
Immune system disorders	Very rare	Anaphylaxis
Metabolism and nutrition disorders	Very common	Anorexia
	Uncommon	Dehydration, hyperuricaemia
Nervous system disorders	Very common	Headache
	Rare	Neurotoxicity
Cardiac disorders	Common	Congestive heart failure,

		sinus tachycardia, tachydysrhythmias
	Very rare	Atrioventricular block, bundle branch block, myocarditis, pericarditis
Vascular disorders	Common	Haemorrhage, phlebitis, thrombophlebitis
	Uncommon	Shock
	Very rare	Hot flushes, thromboembolism
Gastrointestinal disorders	Very common	Abdominal pain or burning sensation, diarrhoea, mucositis/ stomatitis, nausea, vomiting
	Common	Gastrointestinal tract bleeding
	Uncommon	Oesophagitis, colitis (including severe enterocolitis/neutropenic enterocolitis with perforation)
	Very rare	Erosions/ulceration
Skin and subcutaneous tissue disorders	Very common	Alopecia
	Common	Hypersensitivity of irradiated skin (‘radiation recall reaction’), rash/itch

	Uncommon	Skin and nail hyperpigmentation, urticaria
	Very rare	Acral erythema
Renal and urinary disorders	Very common	Red colour urine for 1 - 2 days after administration
General disorders and administration site conditions	Very common	Fever
Investigations	Common	Reduction in left ventricular ejection fraction, elevation of liver enzymes and bilirubin
	Uncommon	ECG abnormalities

Post-marketing side effects

System organ class	**Side effect**
Blood and lymphatic system disorders	Myelosuppression, prolonged bone marrow depression
Metabolism and nutrition disorders	Hyperglycaemia
Gastrointestinal disorders	Dysphagia
Skin and subcutaneous tissue disorders	Skin changes, local toxicity
General disorders and	Fatigue

administration site conditions	

Undesirable effects are similar in adults and children except a greater susceptibility to anthracycline induced cardiac toxicity of children (see section 4.4).

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Very high doses of ZAVEDOS may cause acute myocardial toxicity within 24 hours and severe myelosuppression within one or two weeks (see section 4.8).

Treatment should be symptomatic and supportive.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Idarubicin, an anthracycline, 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.

Idarubicin acts against murine leukaemia and lymphomas.

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. It is extensively metabolised to an active metabolite, idarubicinol. More specifically, hydroxylation of idarubicin at the C-13 carbonyl group results in the secondary alcohol metabolite, idarubicinol. This pathway of idarubicin biotransformation is mediated by cytosolic NADPH-dependent carbonyl and aldo-keto reductases that catalyse the formation of idarubicinol from its parent compound, idarubicin. This active metabolite which is more slowly eliminated with a plasma half-life ranging between 41 and 69 hours. The medicine is eliminated by biliary and renal excretion, mostly in the form of idarubicinol.

Studies of cellular (nucleated blood and bone marrow cells) medicine concentrations in leukaemic patients have shown that peak intra-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.

Paediatric population

Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin in doses ranging from 15 to 40 mg/m^2 over 3 days 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 days of treatment, exhibiting a median half-life of 43,7 hours (range: 27,8 - 131 hours). In a separate study, pharmacokinetic measurements in 15 paediatric patients receiving oral idarubicin in doses ranging from 30 to 50 mg/m^2 during the 3 days of treatment, the maximum plasma concentration of idarubicin was 10,6 ng/mL (range 2,7 - 16,7 ng/mL at the 40 mg/m^2 dose). The

median terminal half-life of idarubicin of was 9,2 hours (range: 6,4 - 25,5 hours). Significant accumulation of idarubicinol was seen over the 3 day treatment period. The observed terminal half-life value of idarubicin after IV administration was comparable to that following oral administration in paediatric patients.

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

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

Total body clearance values of 30 – 107,9 L/h/m^2 for idarubicin reported for adults are higher than the values of 18 - 33 L/h/m^2 reported for paediatric populations. Although idarubicin has a very large volume of distribution in both adults and children, suggesting that much of the medicine is bound to tissues, the shorter elimination half-life and lower total body clearance are not entirely explained by a smaller apparent volume of distribution in children compared to adults.

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 medicine 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 and 4.4) and idarubicin is contraindicated in patients with severe hepatic and/or renal failure (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ZAVEDOS Powder for solution for injection

Lactose monohydrate

Water for injection

Nitrogen

ZAVEDOS RTU Solution for injection

Glycerol

Water for injection

Hydrochloric acid may be present (for pH adjustment)

6.2 Incompatibilities

ZAVEDOS should not be mixed with other medicines. Contact with any solution of an alkaline pH should be avoided as it will result in degradation of the medicine.

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

6.3 Shelf life

36 months

ZAVEDOS powder for solution for injection

Reconstituted solution for injection

Should not be stored for longer than 24 hours at room temperature at or below 25 °C, or 48 hours in a refrigerator at 2 °C - 8 °C.

ZAVEDOS RTU solution for injection

RTU solution in 0,9 % sodium chloride infusion:

ZAVEDOS RTU Solution for injection is intended for single use only and any unused portion should be discarded.

ZAVEDOS RTU Solution for injection and the infusion solutions prepared therefrom, contain no antimicrobial agents. It is therefore recommended that in order to reduce any microbiological hazards, further dilution be effected immediately prior to use and infusion be commenced as soon as practicable after preparation of the admixture. Infusion should be completed within 24 hours of preparation and the residue discarded.

6.4 Special precautions for storage

ZAVEDOS Powder for solution for injection

Store at or below 25 °C.

Protect from light.

ZAVEDOS RTU Solution for injection

RTU solution in vial

Store in a refrigerator at 2 °C - 8 °C and protect from light.

6.5 Nature and contents of container

ZAVEDOS Powder for solution for injection

Vials containing 5 mg and 10 mg idarubicin hydrochloride.

ZAVEDOS RTU Solution for injection

One single-use vial containing 5 mg, 10 mg and 20 mg idarubicin hydrochloride. Each polypropylene vial is closed with a rubber stopper and an aluminium overseal with a purple plastic flip-off top. The vial is packed into an outer cardboard carton.

6.6 Special precautions for disposal and other handling

Preparation of the solution

ZAVEDOS 5 mg and 10 mg Powder for solution for injection must be reconstituted with 5 and 10 mL respectively

of water for injections only. The resulting solution is hypotonic and the recommended administration procedure described in section 4.2 must be followed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27 (0)11) 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

ZAVEDOS 5 mg: Y/26/16

ZAVEDOS 10 mg: Y/26/17

ZAVEDOS RTU 5: 33/26/0211

ZAVEDOS RTU 10: 33/26/0212

ZAVEDOS RTU 20: 33/26/0213

9. DATE OF FIRST AUTHORISATION

ZAVEDOS 5 mg and 10 mg: 08 January 1991

ZAVEDOS RTU 5, 10 and 20: 07 August 2002

10. DATE OF REVISION OF THE TEXT

15 July 2021

BOTSWANA: S2

ZAVEDOS 5 mg - Reg. No.: B9321085

ZAVEDOS 10 mg - Reg. No.: B9321090