SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ZAVEDOS® 5 mg (Intravenous Injection)

ZAVEDOS® 10 mg (Intravenous Injection)

COMPOSITION:

Vials:

Vials containing 5 mg and 10 mg idarubicin hydrochloride.

Excipients: Lactose monohydrate; Water for injection and nitrogen.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Idarubicin, an anthracycline, is a DNA intercalating agent, which interacts with topoisomerase II and has an inhibitory effect on nucleic acid synthesis. Idarubicin has a high potency and is an effective agent against murine leukaemia and lymphomas both by intravenous and oral route. The modification in position 4 of the anthracycline structure gives the compound a high lipophilicity which results in an increased rate of cellular uptake.

Pharmacokinetics

After oral administration to patients with normal renal and hepatic function, idarubicin is rapidly absorbed, with a peak time of 2 - 4 hours; is eliminated from systemic circulation with a terminal plasma half-life (t½) ranging between 10 - 35 hours and is extensively metabolised to an active metabolite, idarubicinol, which is more slowly eliminated with a plasma t½ ranging between 33 and 60 hours. Idarubicin is mostly eliminated by biliary excretion, mainly in the form of idarubicinol; urinary excretion accounting for 1 - 2 % of the dose as unchanged medicine and for up to 4,6 % as idarubicinol.

Average values of absolute bioavailability have been shown to range between 18 and 39 % (individual values observed in the studies ranged between 3 and 77 %), whereas the average values calculated on the data from the active metabolite, idarubicinol, are somewhat higher (29 - 58 %; extremes 12 - 153 %).

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. The capsules are to be used when the intravenous route is not considered suitable.

CONTRA-INDICATIONS:

Severe renal and liver impairment.

Patients with uncontrolled infections.

Pre-existing bone marrow suppression induced by previous drug therapy or radiotherapy.

Hypersensitivity to idarubicin and/or other anthracyclines.

Severe myocardial insufficiency.

Severe dysrhythmias.

Recent myocardial infarction.

Pregnancy and lactation.

WARNINGS:

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

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 haematologic monitoring including granulocytes, red cells and platelets is required. Facilities with laboratory and supportive resources adequate to monitor tolerability to the medicine, and to protect and maintain the patient compromised by toxicity should be available.

Myocardial toxicity, as manifested by potentially fatal congestive heart failure (CHF), acute life threatening dysrhythmias or other cardiomyopathies, may occur during, or several weeks or years after termination of therapy. Should CHF occur, treatment with digitalis, diuretics, sodium restriction and bed rest is indicated.

The risk is directly related to the dose given.

Cumulative dose limits for IV or oral idarubicin have not been identified. However, idarubicin-related cardiomyopathy was reported in 5 % of patients who received cumulative IV doses of 150 to 290 mg/m^2. Available data on patients treated with oral idarubicin total cumulative doses up to 400 mg/m^2 suggest that it is the accepted upper limit of cumulative dose for cardiotoxicity.

ZAVEDOS should be used with caution in the treatment of patients with impaired cardiac function.

Cardiac function should be carefully monitored during treatment in order to minimize the risk of

cardiac toxicity of the type described for anthracycline compounds. An electrocardiogram (ECG) or echocardiogram and a determination of left ventricular ejection fraction (LVEF) should be performed prior to starting, and during, treatment and with follow-up treatments.

The risk of such myocardial toxicity may be higher following concomitant or previous radiation to the mediastinal-pericardial area, or treatment with other potentially cardiotoxic agents, or in patients with a 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 (CHF), cardiomyopathy induced by anthracyclines is usually associated with persistent QRS voltage reduction, increases beyond normal limits of the systolic time interval (PEP/LVEF) and significant decrease of the left ventricular ejection fraction (LVEF) from pretreatment baseline values. Early clinical diagnosis of drug-induced myocardial damage appears to be important for pharmacological treatment to be useful.

In renal and liver impairment kidney and liver functions should be evaluated prior to and during treatment. Treatment should be withheld if bilirubin levels exceed 34 µmol/l (2 mg/100 ml) and/or creatinine serum levels exceed 177µmol/l (2 mg/100 ml).

INTERACTIONS:

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. The use of ZAVEDOS in combination chemotherapy with other potentially cardiotoxic medicines, as well as the concomitant use of other cardioactive compounds, requires monitoring of cardiac function throughout treatment.

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 medicines with the ability to suppress cardiac contractility or cardiotoxic medicines (e.g. trastuzumab). ZAVEDOS should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving ZAVEDOS 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 half-life of trastuzumab is approximately 28,5 days and may persist in the circulation for up to 24 weeks. Therefore medical practitioners should avoid ZAVEDOS therapy for up to 24 weeks after stopping trastuzumab when possible. If ZAVEDOS is used before this time, careful monitoring of cardiac function is recommended.
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.

PREGNANCY AND LACTATION:

Impairment of fertility: ZAVEDOS can induce chromosomal damage in human spermatozoa. For this reason, males undergoing treatment with ZAVEDOS should use effective contraceptive methods.

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 be advised to avoid becoming pregnant during treatment. (See CONTRAINDICATIONS)
The patient should be informed of the potential hazard to the foetus.

Lactation: It is not known whether ZAVEDOS or its metabolites are excreted in human breast milk. Mothers should be advised not to breast-feed while undergoing chemotherapy with ZAVEDOS. (See CONTRAINDICATIONS)

DOSAGE AND DIRECTIONS FOR USE:

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

ZAVEDOS Injection: 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.

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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The following adverse events have been reported in association with ZAVEDOS therapy:

Infections and infestations:

Frequency unknown: infection, severe and sometimes fatal sepsis/septicaemia

Neoplasms benign, malignant and unspecified:

Frequency unknown: secondary leukaemias (acute myeloid leukaemia and myelodysplastic syndrome)

Blood and lymphatic system disorders:

Frequency unknown: anaemia, leukopenia, neutropenia, thrombocytopenia, myelosuppression. prolonged bone marrow depression

Immune system disorders:

Frequency unknown: anaphylaxis

Metabolism and nutrition disorders:

Frequency unknown: anorexia, dehydration, hyperuricaemia, hyperglycaemia

Cardiac disorders:

Frequency unknown: atrioventricular block, bundle branch block, congestive heart failure, myocarditis, pericarditis, sinus tachycardia, tachydysrhythmias

Vascular disorders:

Frequency unknown: headache, haemorrhage, hot flushes, phlebitis, shock, thrombophlebitis, thromboembolism

Gastrointestinal disorders:

Frequency unknown: abdominal pain or burning sensation, colitis (including severe enterocolitis/neutropenic enterocolitis with perforation), diarrhoea, erosions/ulceration, oesophagitis, gastrointestinal tract bleeding, mucositis/stomatitis, nausea, vomiting, dysphagia

Skin and subcutaneous tissue disorders:

Frequency unknown: acral erythema, alopecia, hypersensitivity of irradiated skin, local toxicity, rash/itch, skin changes, skin and nail hyperpigmentation, urticaria

Renal and urinary disorders:

Frequency unknown: red colour urine for 1 - 2 days after administration.

Central nervous system disorders:

Frequency unknown: neurotoxicity

General disorders and administration site conditions:

Frequency unknown: fever, fatigue

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

Special Precautions:

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 agents, 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.

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. In patients with active gastrointestinal disease with increased risk of bleeding and/or perforation, the medical practitioner must balance the benefit or oral ZAVEDOS therapy against the risk.

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.

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

Tumor lysis syndrome: ZAVEDOS may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells. 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 tumor lysis syndrome.

Immunosuppressant effects/increased susceptibility to infections:

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents 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.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

If overdosage with the capsules should occur, gastric lavage should be carried out as soon as possible. The patient should be observed for possible gastro-intestinal 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. 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.

IDENTIFICATION:

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

PRESENTATION:

Vials containing 5 mg and 10 mg idarubicin hydrochloride.

STORAGE INSTRUCTIONS:

Freeze-dried powder for injection:

Store at or below 25 °C and protect from light. Keep well closed.

Reconstituted solution for injection:

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ZAVEDOS® 5 mg Injection: Y/26/16

ZAVEDOS® 10 mg Injection: Y/26/17

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd
85 Bute Lane
Sandton 2196
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

11 October 2013

ZAVEDOS® 5 mg (Intravenous Injection)

BOTSWANA: S2
Reg No.: B9321085

ZAVEDOS® 10 mg (Intravenous Injection)

BOTSWANA: S2
Reg No.: B9321090