ZAVEDOS® CS

1. NAME OF THE MEDICINAL PRODUCT

Zavedos® CS.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Idarubicin Hydrochloride is available as:

Solution for Injection 5 mg/5 mL & 10 mg/10 mL.

Chemical name:

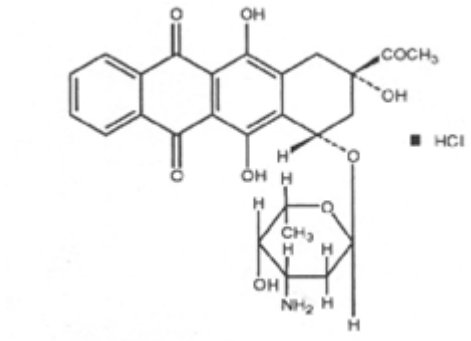
(7S,9S)-9-acetyl-7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-7-*O*-(2,3,6-trideoxy-3-amino-∝-L-lyxo-hexopyranosyl)-5,12-naphthacenedione hydrochloride.

CAS No: 57852-57-0

Description

Idarubicin hydrochloride is a semi synthetic antineoplastic anthracycline for intravenous. Zavedos solution for injection consists of idarubicin hydrochloride as a sterile, pyrogen free, orange-red, clear, mobile solution in vials for intravenous administration.

Structural Formula



3. PHARMACEUTICAL FORM

Sterile solution for injection.

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 may be used in combination chemotherapy regimens involving other cytotoxic agents.

4.2. Posology and method of administration

For induction therapy in adult patients with AML, the following dose schedules are recommended: Zavedos 12 mg/m^2 daily for three days by slow (10-15 min) intravenous injection in combination with Ara-C, 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.

Dose Modifications

Liver 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 impairment of the liver. With anthracyclines a 50% dose reduction is generally used if bilirubin levels are in the range 1.2 to 2.0-mg%.

In case of moderate renal impairment, caution is recommended in the dosage administration (refer to Section 5.2. Pharmacokinetic properties).

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.

Administration

Zavedos injection must be administrated 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 (1/2 hours immediately, then 1/2 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.

It is 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 any residue discarded.

4.3. Contraindications

- Severe renal and liver impairment or patients with uncontrolled infections.
- Hypersensitivity to idarubicin or any other component of the product, other anthracyclines.
- Severe myocardial insufficiency.
- Recent myocardial infarction.
- Severe arrhythmias.
- Persistent myelosuppression.
- Previous treatment with maximum cumulative doses of idarubicin hydrochloride and/or other anthracyclines and anthracenediones (see Section 4.4. Special warnings and precautions for use).

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. 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.

Like most other cytotoxic agents, idarubicin has mutagenic properties and is carcinogenic in rats.

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.

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.

Cardiac Function

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

Early (i.e., Acute) Events. Early cardiotoxicity of idarubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities, such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. 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 (i.e., Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart

failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly, hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cumulative dose limits for IV or oral idarubicin hydrochloride have not been defined. However, idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative IV doses of 150 to 290 mg/m^2. Available data on patients treated with oral idarubicin hydrochloride total cumulative doses up to 400 mg/m^2 suggest a low probability of cardiotoxicity.

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 Multi-Gated radionuclide angiography (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. Interaction with other medicinal products and other forms of interaction). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is variable. Trastuzumab may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

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.

An electrocardiogram or echocardiogram and a determination of left ventricular ejection fraction should be performed prior to starting therapy and during treatment with Zavedos. Early clinical diagnosis of drug-induced myocardial damage appears to be important for pharmacological treatment to be useful.

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.

Hematologic Toxicity

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

Secondary Leukemia

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

Gastrointestinal

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

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.

Hepatic and/or Renal Function

Since impairment of hepatic or renal function may 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. Idarubicin is contraindicated in severe hepatic and renal impairment. In a number of Phase III clinical trials, treatment was contraindicated if bilirubin and/or creatinine serum levels exceeded 2.0 mg%. With other anthracyclines a 50% dose reduction is generally used if bilirubin levels are in the range 1.2 to 2.0 mg% (see Section 4.2. Posology and method of administration).

Tumor Lysis Syndrome

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

Extravasation

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. Posology and method of administration).

Effects at Site of Injection

Phlebosclerosis may result from an injection into a small vessel or from previous injections into the same vein. Following the recommended administration procedures may minimize the risk of

phlebitis/thrombophlebitis at the injection site (see Section 4.2. Posology and method of administration).

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.

Embryo-fetal Toxicity

Idarubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with idarubicin. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available (see Sections 4.6. Fertility, pregnancy and lactation and 5.3. Preclinical safety data).

Other

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

4.5. Interaction with other medicinal products and other forms of interaction

Idarubicin is a potent myelosuppressant and combination chemotherapy regimens that contain other agents with similar action may lead to additive toxicity, especially with regard to bone marrow/hematologic and gastrointestinal effects (see Section 4.4. Special warnings and precautions for use). The use of idarubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.

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.

4.6. Fertility, pregnancy and lactation

Impairment of Fertility

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

Pregnancy

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

Idarubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The patient should be informed of the potential hazard to the fetus.

Women of Childbearing Potential/Contraception in Males and Females

Women of childbearing potential should be advised to avoid becoming pregnant during treatment. Women of childbearing potential should be advised to use effective contraception during treatment with idarubicin and for at least 6.5 months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with idarubicin and for at least 3.5 months after the last dose.

Lactation

It is not known whether idarubicin or its metabolites are excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from idarubicin, advise lactating women not to breastfeed during treatment with idarubicin and for at least 14 days after last dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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/m^2 i.v. (3 days/week for 13 weeks). These effects were not readily reversible after an eight week recovery period.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

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

Infections and infestations: infection, sepsis/septicemia.
Neoplasms benign, malignant and unspecified: secondary leukemias (acute myeloid leukemia and myelodysplastic syndrome).
Blood and lymphatic system disorders: anemia, leukopenia, neutropenia, thrombocytopenia.
Immune system disorders: anaphylaxis.
Metabolism and nutrition disorders: anorexia, dehydration, hyperuricemia.
Cardiac disorders: atrioventricular block, bundle branch block, congestive heart failure, myocarditis, pericarditis, sinus tachycardia, tachyarrhythmias.
Vascular disorders: hemorrhage, hot flashes, phlebitis, shock, thrombophlebitis, thromboembolism.
Gastrointestinal disorders: abdominal pain or burning sensation, colitis (including severe enterocolitis/neutropenic enterocolitis with perforation), diarrhea, erosions/ulceration, esophagitis, gastrointestinal tract bleeding, mucositis/stomatitis, nausea, vomiting.
Skin and subcutaneous tissue disorders: acral erythema, alopecia, hypersensitivity of irradiated skin (‘radiation recall reaction’), local toxicity, rash/itch, skin changes, skin and nail hyperpigmentation, urticaria.
Renal and urinary disorders: red color to the urine for 1-2 days after administration.
General disorders and administration site conditions: fever.
Investigations: asymptomatic reductions in left ventricular ejection fraction, ECG abnormalities, elevation of liver enzymes and bilirubin.

4.9. Overdose

There is no known antidote to Zavedos. Very high doses of idarubicin may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression within one or two weeks. Overdose may possibly result in increased severity of gastrointestinal toxicity.

Treatment should aim to support the patient during this period and should utilise such measures as blood transfusions, reverse-barrier nursing, antibiotics and symptomatic treatment of mucositis.

It is anticipated that overdosage with idarubicin may cause acute cardiac toxicity and may be associated with a higher incidence of delayed cardiac failure. Delayed cardiac failure has been seen with the anthracyclines up to several months after the overdose.

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 multicompartment 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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.

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 antitumour activities in experimental models both *in vitro* and *in vivo*. In the rat, idarubicinol, administered the same doses as the parent drug, is 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.

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

Special Populations

Hepatic and renal impairment

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

Pediatric

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

5.3. Preclinical safety data

Idarubicin was genotoxic in most of the *in vitro* or *in vivo* tests performed. Intravenous idarubicin was carcinogenic, toxic to the reproductive organs, and embryotoxic and teratogenic in rats. No

noteworthy effects on the mothers or offspring were seen in rats given intravenous idarubicin during the peri- and post-natal periods up to the dose of 0.2 mg/kg/day. It is not known whether the compound is excreted in breast milk. Intravenous idarubicin, like other anthracyclines and cytotoxic drugs, was carcinogenic in rats. A local safety study in dogs showed that extravasation of the drug causes tissue necrosis.

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Zavedos solution for injection is available in two sizes of single use only plastic Cytosafe® vials:
5 mg: The vial contains 5 mg of idarubicin hydrochloride, 125 mg glycerol, Water for Injections q.s to 5 mL and HCl to pH 3.5.
10 mg: The vial contains 10 mg of idarubicin hydrochloride, 250 mg glycerol, Water for Injections q.s to 10 mL and HCl to pH 3.5.

6.2. Incompatibilities

Idarubicin should not be mixed with other drugs. Contact with any solution of an alkaline pH should be avoided as it will result in degradation of the drug. Idarubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

6.3. Shelf life

Zavedos solutions for injection are physically and chemically stable for 36 months under refrigeration (2°C-8°C) and protected from light.

6.4. Special precautions for storage

Zavedos solution for injection - store at 2°C-8°C (Refrigerate. Do not freeze). Protect from light.

6.5. Special precautions for disposal and handling

Protective Measures. 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.
- Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution, medical attention should be sought.
- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.
- Discard any unused solution.

7. MARKETING AUTHORISATION HOLDER

Pfizer (Thailand) Limited

Warning (based on the Ministry of Public Health’s Announcement)

This drug may cause serious harm, should be used under the supervision of a physician.

LPD Revision No.: 7.0

LPD Date: September 30, 2021

Country: Thailand