SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zavedos® 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains10mg idarubicin hydrochloride.
The reconstituted solution contains 1mg/ml.
Excipients with known effect:
Each vial contains 100mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

Sterile, pyrogen-free, orange-red, freeze-dried powder in vial containing 10mg of idarubicin hydrochloride, with 100mg of lactose anhydrous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antimitotic and cytotoxic agent. Acute non-lymphocytic leukemia (ANLL) in adults for remission induction in untreated patients or for remission induction in relapsed or refractory patients. Acute lymphocytic leukemia (ALL) as second- line treatment in adults and children.

4.2 Posology and method of administration

For intravenous use only.
Not for intrathecal use.

Dosage is calculated on the basis of body surface area.

Acute non- lymphocytic leukaemia (ANLL)
Adults
- 12 mg/m^2/day i.v. daily for 3 days in combination with cytarabine.
or
- 8 mg/m^2/day i.v. daily for 5 days with/without combination.

Acute lymphocytic leukaemia (ALL)

Adults
As single agent in ALL the suggested dose in adults is 12 mg/m^2 i.v. daily for 3 days.

Children
10 mg/m^2 i.v. daily for 3 days, as a single agent.

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

Administration of a second course should be delayed in patients who develop severe mucositis until recovery from this toxicity has occurred and a dose reduction of 25% is recommended.

For directions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

- known hypersensitivity to the active substance or to any of the excipients listed in section 6.1, and/or to other anthracyclines or anthracenediones,
- its use should be avoided in patients with heart disease and myocardial failure,
- severe renal impairment,
- severe hepatic impairment,
- uncontrolled infections,
- breast-feeding (see section 4.6),
- attenuated live vaccines (against yellow fever, chickenpox, herpes zoster, measles, mumps, rubella, tuberculosis, rotavirus, influenza) and for the 6 months following the discontinuation of chemotherapy (see section 4.5),
- severe heart failure,
- myocardial infarction in the previous six months,
- severe cardiomyopathy,
- severe arrhythmia,
- persistent myelosuppression,
- previous treatment with idarubicin hydrochloride and/or other anthracyclines or anthracenediones at the maximum cumulative dose (See section 4.4).

4.4 Special warnings and precautions for use

General

ZAVEDOS for injection must be administered by the intravenous route only.

ZAVEDOS administration must be monitored by a qualified doctor with experience of cytotoxic therapies.

Before starting treatment with ZAVEDOS, patients must be free from the adverse effects of any previous cytotoxic therapy (such as stomatitis, neutropoenia, thrombocytopoenia and generalised infections).

Heart function

Anthracycline treatment is associated with a risk of cardiotoxicity. This may be delayed or appear immediately.

- Immediate cardiotoxicity: primarily presents as sinus tachycardia, ventricular extrasystole, ventricular tachycardia and electrocardiogram abnormalities (T-wave changes, atrioventricular conduction disturbances, branch block).

These effects are not generally predictive of the development of delayed cardiotoxicity, are rarely serious from a clinical perspective and do not generally require discontinuation of the treatment.

- Delayed cardiotoxicity: can develop later during treatment, in the two to three months following the end of treatment or, more rarely, several months or years after the end of treatment.

Delayed cardiomyopathy presents as reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure, such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. Life-threatening congestive heart failure is the most severe form of cardiomyopathy caused by

anthracyclines and represents a cumulative toxicity risk that limits the maximum dose of this medicinal product.

The maximum cumulative dose of idarubicin hydrochloride has not been defined, but at a dose of 93 mg/m^2, no changes in heart function have been reported. However, cardiomyopathy linked to idarubicin hydrochloride was reported in 5% of patients who received a cumulative intravenous dose of 150 to 290 mg/m^2. The available data on patients treated with oral idarubicin hydrochloride up to a dose of 400 mg/m^2 suggest that there is a low probability of cardiotoxicity.

Heart function must be assessed before and throughout treatment, to reduce the risk of severe heart failure.

- Before treatment: clinical assessment, ECG with either ventricular scintigraphy or echocardiography, particularly in patients with risk factors for increased cardiac toxicity: symptomatic or asymptomatic cardiovascular disease, previous or concomitant radiotherapy of the mediastinal/pericardial region, previous treatment with other anthracyclines or anthracenediones, and concomitant use of other medicinal products that can affect cardiac contractility.
- During treatment: regular monitoring of LVEF (assessed using ventricular scintigraphy [MUGA] and/or an echocardiogram [ECHO]), with immediate discontinuation of ZAVEDOS at the first signs of deterioration in function.

LVEF must be measured repeatedly by MUGA or ECHO, particularly when high and cumulative doses of anthracycline are being used. The technique used for the assessment must be reproducible throughout the entire monitoring period.

Heart function must be monitored particularly closely in patients receiving high cumulative doses and in those with risk factors. However, the cardiac toxicity associated with ZAVEDOS can still occur with lower cumulative doses, whether or not risk factors are present.

- Delayed effects: infants and children seem to be more susceptible to anthracycline-induced cardiac toxicity, and their heart function must be monitored regularly over the long term.

The toxicity of ZAVEDOS and other anthracyclines and anthracenediones is likely to be additive.

Anthracyclines, including idarubicin, must not be administered in combination with other cardiotoxic agents (e.g. trastuzumab) without closely monitoring the patient's heart function (see section 4.5).

Patients receiving anthracyclines after discontinuing other cardiotoxic agents, particularly those with a long half-life, such as trastuzumab, may be exposed to an increased risk of cardiotoxicity. As the reported half-life of trastuzumab is variable. The trastuzumab may persist in circulation for up to 7 months after the discontinuation of treatment. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after the discontinuation of trastuzumab when possible. If this is not possible, the patient's cardiac function should be monitored carefully.

Haematological toxicity

Like other cytotoxic agents, ZAVEDOS can cause myelosuppression. The main manifestation of the haematological toxicity of ZAVEDOS is dose-dependent, reversible leukopoenia and/or neutropoenia. This myelosuppression is also the most common form of dose-limiting toxicity. Leukopoenia and neutropoenia generally reach their lowest point between the 10th and 14th days of treatment; leukocyte/neutrophil counts generally return to normal around the 21st day. Thrombocytopoenia and anaemia can also occur.

The clinical consequences of severe myelosuppression include fever, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia and death.

Haematological parameters, including white blood cell count, must be assessed before and during each treatment cycle.

In the absence of sufficient data, the oral administration of ZAVEDOS is not recommended in patients who have undergone total body irradiation or haematopoietic stem cell transplantation.

Secondary leukaemia

Secondary leukaemia, with or without a pre-leukaemic phase, has been reported in patients treated with anthracyclines, including ZAVEDOS. Secondary leukaemia is more common when the product is administered in combination with DNA-altering antineoplastic agents, when patients have been pre-treated with a cytotoxic medicinal product, or when the anthracycline doses have been increased incrementally. This secondary leukaemia can have a latency period of one to three years.

Some forms of leukaemia arising subsequent to the administration of anticancer agents such as ZAVEDOS (see section 4.8) can be cured if treated promptly and appropriately. Haematological monitoring is therefore required for all patients treated with ZAVEDOS.

Gastrointestinal toxicity

ZAVEDOS is an emetic. Mucositis (generally stomatitis, less commonly oesophagitis) generally appears at the start of treatment. If severe, it can develop into ulceration of the mucous membrane within a few days. The majority of patients recover at around the third week of treatment.

Severe gastrointestinal events (such as perforation and bleeding) have occasionally been observed in patients treated orally with ZAVEDOS who have acute leukaemia, or who have another disease or have previously taken a different treatment known to cause gastrointestinal complications.

In patients with an active gastrointestinal disease that entails an increased risk of bleeding and/or perforation, the doctor must assess the risk-benefit ratio of oral ZAVEDOS administration.

Hepatic and/or renal function

Since hepatic and/or renal impairment can affect the metabolism of idarubicin, hepatic and renal function (serum bilirubin and serum creatinine levels) must be assessed before and during treatment. In a number of phase III clinical studies, treatment with ZAVEDOS was contraindicated where serum bilirubin and/or creatinine levels exceeded 2.0 mg/dL.

In the absence of pharmacokinetic data, oral administration of idarubicin is not recommended if the patient has even moderate hepatic and/or renal impairment.

Injection site effects

Sclerosis may appear in small vessels or following repeat injections into the same vein. Compliance with the administration guidelines can reduce the risk of phlebitis and thrombophlebitis at the injection site (see section 4.2).

Extravasation

Extravasation of ZAVEDOS during intravenous injection can cause local pain, severe tissue damage (blistering, severe inflammation of subcutaneous tissue) and necrosis. If these signs appear during intravenous injection of ZAVEDOS, discontinue the administration immediately.

In the case of extravasation, dexrazoxane may be used preventatively or to reduce tissue damage.

Tumour lysis syndrome

ZAVEDOS can induce hyperuricaemia due to the increased purine catabolism that occurs during the rapid lysis of neoplastic cells (tumour lysis syndrome) following treatment administration. The levels of uric acid, potassium, calcium, phosphates and creatinine in the blood must be assessed regularly during treatment. Hydration, very careful urine alkalinisation and prophylactic treatment with allopurinol or another urate lowering agent to prevent hyperuricaemia can minimise the potential complications of tumour lysis syndrome.

Immunosuppressant effects/increased susceptibility to infection

Combination with live attenuated vaccines is contraindicated, as it may lead to a potentially fatal generalised vaccine disease (see sections 4.3 and 4.5). Dead or inactivated viral vaccines may be administered, although their efficacy may be diminished.

Before initiating leukaemia treatment, appropriate measures must be taken to control any systemic infections.

Reproductive system

Idarubicin can cause genotoxicity. Men Male and female patients treated with idarubicin hydrochloride are advised to adopt effective contraceptive measures during therapy and for a period after treatment.

Men treated with idarubicin hydrochloride are advised, if appropriate and available, to seek advice on sperm preservation due to the possibility of irreversible infertility caused by the therapy (see section 4.6). Patients desiring to have children after completion of therapy should be advised to discuss with an appropriate specialist first.

Other

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism, have been reported during ZAVEDOS use.

This medicine is not recommended in combination with phenytoin (and, by extrapolation, with fosphenytoin) (see section 4.5).

Patients must be warned that this medicine may cause red-coloured urine 1 to 2 days after its administration.

4.5 Interactions with other medicinal products and other forms of interaction

When combined with other chemotherapies, ZAVEDOS can lead to additive toxicity, particularly with regards to medullary/haematological effects and gastrointestinal effects (see section 4.4). Heart function must be monitored throughout the treatment if ZAVEDOS is used in chemotherapy that also involves other potentially cardiotoxic products, as well as if other products for cardiac disease (e.g. calcium channel blockers) are used concomitantly.

Changes in hepatic or renal function caused by concomitant treatments can affect the metabolism, pharmacokinetics, efficacy and/or toxicity of idarubicin (see section 4.4.).

Additive myelosuppression can appear when radiotherapy takes place concomitantly or two to three weeks before treatment with ZAVEDOS.

INTERACTIONS COMMON TO ALL CYTOTOXIC AGENTS

Contraindicated combinations (see section 4.3)

+ **Live attenuated vaccines (against yellow fever, chickenpox, herpes zoster, measles, mumps, rubella, tuberculosis, rotavirus, influenza)** and for the 6 months following the discontinuation of chemotherapy Risk of potentially fatal generalised vaccine disease.

Inadvisable combinations (see section 4.4)

+ **Olaparib**

Risk of increased cytotoxic myelosuppressive effect.

+ **Phenytoin (and, by extrapolation, fosphenytoin)**

Risk of occurrence of seizures due to decreased gastrointestinal absorption by the cytotoxic agent of phenytoin alone, or risk of an increase in toxicity and a loss of efficacy of the cytotoxic agent due to an increase in the hepatic metabolism by phenytoin or by fosphenytoin.

Associations requiring precautions for use

+ **Antivitamin K**

Increased risk of thrombosis and bleeding in the course of tumour diseases. In addition, possible interaction between the AVK and chemotherapy.

More frequent monitoring of the INR.

Associations to be taken into account

+ **Flucytosine**

Risk of increased haematological toxicity.

+ **Immunosuppressive drugs (ciclosporin, everolimus, sirolimus, tacrolimus, temsirolimus).**

Excessive immunodepression with a risk of lymphoproliferative syndrome.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount data from the use of idarubicin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Idarubicin should not be used during pregnancy unless only if the potential benefit justifies the potential risk to the foetus. The patient should be informed of the potential hazard to the foetus.

Women of childbearing potential/ Contraception in males and females

Women of child bearing potential should be advised not to become pregnant and 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 (see section 4.4).

Breast-feeding

It is not known whether idarubicin passes into breast milk. As other anthracyclines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from idarubicin, women should be advised not to breastfeed during treatment with idarubicin and for at least 14 days after the last dose.

Fertility

Idarubicin can cause chromosome damage in human spermatozoa and/or infertility. For these reasons, men treated with idarubicin should use effective contraceptive methods for at least 3.5 months after the last dose (see section 4.4). Both men and women should seek advice on fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

The effects of ZAVEDOS on the ability to drive vehicles and use machines have not been systematically evaluated.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. The frequency grouping is defined using the following convention: 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); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations:
Very common: Infection.
Uncommon: Sepsis/septicaemia.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps):
Uncommon: Secondary leukaemia (acute myeloid leukaemia and myelodysplastic syndrome).

Blood and lymphatic system disorders:
Very common: Anaemia, leukopoenia, neutropoenia, febrile neutropoenia, pancytopoenia, thrombocytopoenia.

Immune system disorders:
Very rare: Anaphylaxis.

Metabolism and nutrition disorders:
Very common: Anorexia.
Uncommon: Hyperuricaemia (tumour lysis syndrome), dehydration.
Unknown frequency: Hyperphosphatemia, hyperkalaemia, hypocalcaemia, hyperphosphaturia (tumour lysis syndrome).

Cardiac disorders:
Very common: Sinus tachycardia, tachyarrhythmia, bradycardia, asymptomatic reduced left ventricular ejection fraction.
Common: Cardiomyopathy
Uncommon: ECG abnormalities (including non-specific ST segment changes), myocardial infarction, congestive heart failure.
Very rare: Atrioventricular block, branch block, myocarditis, pericarditis.

Vascular disorders:
Common: Phlebitis, deep vein thrombosis, haemorrhage.
Uncommon: Shock.
Very rare: Hot flushes, pulmonary embolism.

Gastrointestinal disorders:
Very common: Nausea, vomiting and diarrhoea, mucositis/stomatitis, abdominal pain, burning sensations.
Common: Gastrointestinal tract bleeding, colic.
Uncommon: Oesophagitis and colitis (including severe enterocolitis/neutropenic enterocolitis with perforation).
Very rare: Erosion/ulceration.

Skin and subcutaneous tissue disorders:
Local toxicity (frequency not known):
- In the event of extravasation: local pain, severe tissue damage (blistering, severe inflammation of subcutaneous tissue).
- In the event of injection site reaction: sclerosis in small vessels.

Very common: Alopecia.
Common: Rash, pruritus, reactivated skin reactions in irradiated zone.
Uncommon: Urticaria, skin and nail hyperpigmentation, cellulitis that could be severe, tissue necrosis.
Very rare: Acral erythema.

Renal and urinary disorders:
Very common: Red discolouration of urine one to two days after administration.

General disorders and administration site conditions:
Very common: Fever, headaches, chills

Investigations:
Very common: Asymptomatic reduced left ventricular ejection fraction, ECG abnormalities (T-wave abnormality).
Common: Increased hepatic enzymes and bilirubin.

Nervous system disorders
Rare: Cerebral haemorrhage.

Haematopoietic system
Marked myelosuppression is the most severe adverse reaction of treatment with ZAVEDOS. This, however, may be necessary to eradicate leukaemia cells (see section 4.4).

Cardiotoxicity
Life-threatening congestive heart failure is the most severe form of cardiomyopathy induced by anthracyclines and represents cumulative dose-limiting toxicity (see section 4.4).

Description of certain undesirable effects
Gastrointestinal
Stomatitis and, in certain serious cases, ulceration of the mucosa, dehydration due to vomiting and severe diarrhoea; risk of perforated colon.

Other undesirable effects: hyperuricaemia
Preventing the symptoms of hyperuricaemia, with hydration, alkalinisation of the urine and prophylaxis with allopurinol may minimise the potential complications of tumour lysis syndrome.

The undesirable effects are similar in adults and children, except that there is a greater susceptibility to anthracycline-induced cardiac toxicity in children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

Overdose is associated with the risk of acute and delayed myocardial toxicity and a risk of intensified myelosuppression and other adverse events.

Very high doses of idarubicin may be expected to cause acute myocardial toxicity within 24 hours and severe myelosuppression for the following week to two weeks.

Treatment consists in transferring the patient to a specialised unit and maintaining vital functions via blood transfusions and palliative nursing care.

Delayed heart failure has been observed with anthracyclines for up to several months after the overdose.

Patients must therefore be monitored closely and if signs of heart failure are observed, appropriate treatment must be started.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anthracyclines and related substances, ATC Code L01DB06.
(L: antineoplastic agents and immunomodulating agents)

Cytotoxic antibiotic of the anthracycline family.

Idarubicin is a DNA intercalating anthracycline which interacts with the enzyme topoisomerase II and has an inhibitory effect on nucleic acid synthesis.

As a result of modification of position 4 on the anthracycline ring, idarubicin is highly lipophilic. Its cellular uptake is therefore higher than that of doxorubicin or daunorubicin.

The main metabolite, idarubicinol, has shown anti-tumoural activity in experimental models under *in vitro* and *in vivo* conditions.

5.2 Pharmacokinetic properties

After IV administration in patients with normal renal or hepatic function, idarubicin has a terminal half-life T1/2 of between 11 and 25 hours.

97% and 94% of idarubicin and the active metabolite idarubicinol, respectively, are protein bound with a concentration of 10 ng/mL.

The medicine has been assayed in the nucleated blood and bone marrow cells of patients with leukaemia. These studies show that the cellular concentrations of idarubicin reach their maximum a few minutes after injection. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than 100 times greater than the plasma concentrations.

The extremely high total plasma clearance value (0.7 to 0.9 L/min), which is far superior to the expected hepatic rate, indicates slow clearance as a result of the high distribution of the product in the tissues and suggests the presence of extensive extra-hepatic metabolism.

Idarubicin is mostly transformed into an active metabolite, idarubicinol, which has a slower half-life of between 41 and 69 hours.

ZAVEDOS is eliminated from the cells and plasma at a comparably similar speed, and has a terminal half-life of about 15 hours.

Idarubicin undergoes extensive transformation to idarubicinol and is eliminated in the bile and urine.

At-risk populations:

Renal and hepatic impairment

The pharmacokinetics of idarubicin in patients with renal and/or hepatic impairment has not been fully studied. It is likely that, in patients with moderate to severe hepatic dysfunction, the metabolism of idarubicin could be altered, leading to an increase in systemic idarubicin concentrations. Renal impairment can affect the metabolism of idarubicin. The oral administration of idarubicin is therefore not recommended in patients with hepatic and/or renal impairment (see section 4.4) and idarubicin is contraindicated in patients with severe renal or hepatic impairment (see section 4.3).

Paediatric population:

Pharmacokinetic measurements taken from 7 paediatric patients receiving intravenous idarubicin hydrochloride at doses between 15 and 40 mg/m^2 for 3 days showed that the median half-life of idarubicin was 8.5 hours (range: 3.6 – 26.4 hours). The active metabolite, idarubicinol, accumulated over the 3 days of treatment, has a median half-life of 43.7 hours (range: 27.8 – 131 hours). In another study, pharmacokinetic measurements taken from 15 paediatric patients receiving idarubicin hydrochloride orally at doses between 30 and 50 mg/m² for 3 days showed that the peak plasma concentration of idarubicin hydrochloride was 10.6 ng/ml (range: 2.7 – 16.7 ng/ml at the dose of 40 mg/m^2). The median terminal half-life of idarubicin was 9.2 hours (range: 6.4 – 25.5 hours). A significant accumulation of idarubicinol was observed over the 3-day treatment period. The terminal half-life of idarubicin observed after intravenous administration was comparable to that observed after oral administration in paediatric patients.

In adults, after oral administration of 10 to 60 mg/m^2 of idarubicin hydrochloride, the idarubicin hydrochloride was rapidly absorbed, with peak plasma concentrations of 4 to 12.65 ng/ml reached at 1 to 4 hours after administration. The terminal half-life was 12.7 ± 6 hours (mean ± SD). After the intravenous administration of idarubicin in adults, the terminal half-life was 13.9 ± 5.9 hours, and comparable to that observed after oral administration.

As the C_{max} of idarubicin is comparable in children and adults after oral administration, absorption kinetics do not appear to be different in these two populations.

After both oral and intravenous administration, the elimination half-life values of idarubicin are different in children and adults:

Total body clearance values of idarubicin between 30 and 107.9 l/h/m² observed in adults are higher than the values ranging from 18 to 33 l/h/m² observed in the paediatric population. Although the volume of distribution of idarubicin is very high in both adults and children, suggesting that most of the medicine binds to tissues, the shorter elimination half-life and the lower total body clearance cannot be fully explained by an apparent volume of distribution lower in children than in adults.

5.3 Preclinical Safety Data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

6.2 Incompatibilities

The product precipitates when combined with heparin.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Unreconstituted solution: Store below 25^0C.

Reconstituted solution: Use immediately after reconstitution.

6.5 Nature and contents of container

Colourless glass vial
Zavedos® 10mg Powder for Solution for Injection vials are available as single vials.

6.6 Special precautions for disposal and other handling

The following protective recommendations are given due to the toxic nature of this substance:

- This product should be handled only by personnel who have been trained in the safe handling of such preparations.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling Zavedos® should wear protective clothing: goggles, gowns and disposable gloves and masks.
- All items used for administration or cleaning, including gloves, should be placed in high risk, waste disposal bags for high temperature incineration.
- The reconstituted solution is hypotonic and the recommended administration procedure described below must be followed.

Reconstitute with 10ml of Water for Injections to produce a 1mg/ml solution for injection (i.v.). The reconstituted solution is clear red-orange solution, essentially free from visible foreign matter, see section 6.4 also.

Intravenous administration: Zavedos®, as the reconstituted solution, must be administered only by the intravenous route. A 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.

All cleaning materials should be disposed of as indicated previously. Accidental contact with the skin and eyes should be treated immediately by copious lavage with water or sodium bicarbonate solution, medical attention should be sought.
Discard any unused solution.

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

9. LICENSE NUMBER

059-92-27176

Revised in 06/2023 according to MOH guidelines.