SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zavedos 10 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Idarubicin Hydrochloride 10.0 mg HSE

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Opaque red cap and white body, self-locking, hard gelatin capsule, size no. 4, containing an orange powder.

4.1 Therapeutic indications

Acute non-lymphocytic leukaemia (ANLL).

Whenever intravenous idarubicin hydrochloride cannot be employed e.g. for medical, psychological or social reasons, oral idarubicin can be used for remission induction in patients with previously untreated, relapsed or refractory acute non-lymphocytic leukaemia.

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

As a single agent in the treatment of advanced breast cancer after failure of front line chemotherapy not including anthracyclines.

4.2 Posology and method of administration

Route of Administration: Oral

Dosage is usually calculated on the basis of body surface area.

In adult acute non-lymphocytic leukaemia (ANLL) also referred to as acute myelogenous leukaemia (AML), the recommended dose schedule suggested is

30mg/m^2 orally given daily for 3 days as a single agent, or between 15 and 30mg/m^2 orally daily for 3 days in combination with other anti-leukemic agents.

In advanced breast cancer the recommended dose schedule as single agent is 45mg/m^2 orally given either on a single day or divided over 3 consecutive days, to be repeated every 3 or 4 weeks based on the haematological recovery.

A maximum cumulative dose of 400mg/m^2 is recommended.

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.

In patients with hepatic impairment a dose reduction of Zavedos should be considered. (See section 4.4).

The capsules should be swallowed whole with some water and should not be sucked, bitten or chewed. Zavedos Capsules may also be taken with a light meal.

4.3 Contraindications

- hypersensitivity to idarubicin or to any of the excipients listed in section 6.1, other anthracyclines or anthracenediones
- severe hepatic impairment
- severe renal impairment
- uncontrolled infections
- severe cardiomyopathy
- 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)
- breast-feeding should be stopped during drug therapy (see section 4.6)

4.4 Special warnings and precautions for use

General

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

This ensures that immediate and effective treatment of severe complications of the disease and/or its treatment (e.g. haemorrhage, overwhelming infections) may be carried out.

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

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

Cumulative dose limits for 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 Multiple Gated Acquisition (MUGA) scan or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended,

especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g. trastuzumab). Anthracyclines including idarubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see section 4.5). 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. The substance may persist in circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If this is not possible, the patient's cardiac function should be monitored carefully.

Cardiac function monitoring must be particularly strict in

patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with idarubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

In infants and children there appears to be a greater susceptibility to anthracycline induced cardiac toxicity, and a long-term periodic evaluation of cardiac function has to be performed. It is probable that the toxicity of idarubicin and other anthracyclines or anthracenediones

is additive.

Haematologic Toxicity

Idarubicin is a potent bone marrow suppressant. Severe myelosuppression will occur in all patients given a therapeutic dose of this agent.

Haematologic profiles should be assessed before and during each cycle of therapy with idarubicin, including differential white blood cell (WBC) counts.

A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of idarubicin hematologic toxicity and is the most common acute doselimiting toxicity of this drug.

Leukopenia and neutropenia are usually severe; thrombocytopenia and anaemia may also occur. Neutrophil and platelet counts usually reach their nadir 10 to 14 days after drug administration; however, cell counts generally return to normal levels during the third week.

During the phase of severe myelosuppression, deaths due to infections and/or haemorrhages have been reported.

Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death. If febrile neutropenia occurs, treatment with an IV antibiotic is recommended.

Secondary Leukaemia

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

Gastrointestinal

Idarubicin is emetigenic. Mucositis (mainly stomatitis, less often

oesophagitis) generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Occasionally, episodes of serious gastrointestinal events (such as perforation or bleeding) have been observed in patients receiving oral idarubicin who had acute leukaemia or a history of other pathologies or had received medications known to lead to gastrointestinal complications. In patients with active gastrointestinal disease with increased risk of bleeding and/or perforation, the physician must balance the benefit of oral idarubicin therapy against the risk.

Hepatic and/or Renal Function

Since hepatic and/or renal function impairment can affect the disposition of idarubicin, liver and kidney function should be evaluated with conventional clinical laboratory tests (using serum bilirubin and serum creatinine as indicators) prior to, and during, treatment. In a number of Phase III clinical trials, treatment was contraindicated if bilirubin and/or creatinine serum levels exceeded 2.0-mg %. With other anthracyclines a 50% dose reduction is generally used if bilirubin levels are in the range 1.2 to 2.0-mg %.

Tumour Lysis Syndrome

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

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines (like yellow fever) 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.

Reproductive system

Idarubicin can cause genotoxicity. 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 coincidentally reported with the use of idarubicin.

The product may cause a red colouration of the urine for 1 - 2 days after administration and patients should be advised of this fact.

4.5 Interaction with other medicinal products and other forms of interaction

Idarubicin is a potent myelosuppressant and combination chemotherapy regimens including other agents with similar action may be expected to induce additive myelosuppressant effects (see section 4.4). 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).

An additive myelosuppressant effect may occur when radiotherapy is given concomitantly or within 2-3 weeks prior to treatment with idarubicin.

Concomitant use of live attenuated vaccines (e.g. yellow fever) is not recommended, due to a risk of possibly fatal systemic disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. An inactivated vaccine should be used if available.

At combination of oral anticoagulants and anticancer chemotherapy, increased frequency of the INR (International Normalised Ratio) monitoring is recommended, since the risk for an interaction cannot be excluded.

Cyclosporin A: The coadminstration of cyclosporin A as a single chemosensitizer significantly increased idarubicin AUC (1.78-fold) and idarubicinol AUC (2.46-fold) in patients with acute leukaemia. The clinical significance of this interaction is unknown.

A dosage adjustment may be necessary in some patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of 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 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 childbearing 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 or its metabolites are excreted in human 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 induce chromosomal damage in human spermatozoa. Both men and women should seek advice on fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of undesirable effects are based on the following categories:

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)

Not known (cannot be estimated from the available data)

Infections and infestations

Very common	Infections

Uncommon	Sepsis, septicaemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Secondary leukaemia (acute myeloid leukaemia and myelodysplastic syndrome)
Blood and lymphatic system disorders	
Very common	Anaemia, severe leukopenia and neutropenia, thrombocytopenia
Not known	Pancytopenia
Immune system disorders	
Very rare	Anaphylaxis
Endocrine disorders	
Very common	Anorexia
Uncommon	Dehydration
Metabolism and nutrition disorders	
Uncommon	Hyperuricaemia
Not Known	Tumour Lysis Syndrome
Nervous system disorders	
Rare	Cerebral haemorrhages
Cardiac disorders	
Common	Bradycardia, sinus tachycardia, tachyarrhythmia, asymptomatic reduction of left ventricular ejection fraction, congestive heart failure, cardiomyopathies (see section 4.4 for associated signs and symptoms)
Uncommon	ECG abnormalities (e.g. nonspecific ST segment changes), myocardial infarction
Very rare	Pericarditis, myocarditis, atrioventricular and bundle branch block
Vascular disorders	
Common	Local phlebitis, thrombophlebitis, haemorrhages
Uncommon	Shock
Very rare	Thromboembolism, flush

Gastrointestinal disorders

Very common	Nausea, vomiting, mucositis/stomatitis, diarrhoea, abdominal pain or burning sensation
Common	Gastrointestinal tract bleeding, bellyache
Uncommon	Oesophagitis, colitis (including severe enterocolitis / neutropenic enterocolitis with perforation)
Very rare	Gastric erosions or ulcerations

Hepatobiliary disorders

Common	Elevation of the liver enzymes and bilirubin

Skin and subcutaneous tissue disorders

Very common	Alopecia
Common	Rash, itch, hypersensitivity of irradiated skin ('radiation recall reaction')
Uncommon	Skin and nail hyperpigmentation, urticaria, cellulitis (this event can be severe), tissue necrosis
Very rare	Acral erythema

Renal and urinary disorders

Very common	Red colouration of the urine for 1 – 2 days after the treatment.

General disorders and administration site conditions

Very common	Fever, headache, chills

Description of selected adverse reactions

Haematopoietic system

Pronounced myelosuppression is the most severe adverse effect of idarubicin treatment. However, this is necessary for the eradication of leukemic cells (see section 4.4).

Cardiotoxicity

Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug (see section 4.4).

Gastrointestinal

Stomatitis and in severe cases ulceration of mucosa, dehydration caused by severe vomiting and diarrhoea; risk of perforation of colon etc.

Other adverse reactions: hyperuricaemia

Prevention of symptoms by hydration, urine alkalinisation, and prophylaxis with allopurinol may minimise potential complications of tumour lysis syndrome.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

Delayed cardiac failure has been seen with anthracyclines for up to several months after the overdose.

Patients treated with oral idarubicin should be observed for possible gastrointestinal haemorrhage and severe mucosal damage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Idarubicin is an antimitotic and cytotoxic agent which intercalates with DNA and interacts 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 i.v. and oral routes. Studies *in vitro* on human and murine anthracycline-resistant cells have shown a lower degree of cross-resistance for idarubicin compared with doxorubicin and daunorubicin. Cardiotoxicity studies in animals have indicated that idarubicin has a better therapeutic index than daunorubicin and doxorubicin. The main metabolite, idarubicinol, has shown *in vitro* and *in vivo* antitumoral activity in experimental models. In the rat, idarubicinol, administered at the same doses as the parent drug, is clearly less cardiotoxic than idarubicin.

5.2 Pharmacokinetic properties

After 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 T½ ranging between 10-35 hours and is extensively metabolized to an active metabolite, idarubicinol, which is more slowly eliminated with a plasma T½ ranging between 33 and 60 hours. The drug is mostly eliminated by biliary excretion, mainly in the form of idarubicinol, urinary excretion accounting for 1-2% of the dose as unchanged drug 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 ranging 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%).

Studies of cellular (nucleated blood and bone marrow cells) drug concentrations in leukaemic patients have shown that uptake is rapid and almost parallels the appearance of the drug in plasma. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than two hundred times the plasma concentrations. Idarubicin and idarubicinol disappearance rates in plasma and cells were almost comparable.

5.3 Preclinical safety data

Idarubicin has mutagenic properties and it is carcinogenic in rats.

Reproduction studies in animals have shown that idarubicin is embryotoxic and teratogenic in rats but not rabbits.

6.1 List of Excipients

Microcrystalline cellulose	Ph. Eur.
Glyceryl palmito-stearate	HSE

Capsule shell:

Red iron oxide (E172)	FP
Titanium dioxide (E171)	Ph. Eur.
Gelatin	Ph. Eur.

Printing ink:

Shellac
Black Iron Oxide (E172)
Propylene Glycol
Strong ammonia solution
Potassium hydroxide

6.2 Incompatibilities

Not known.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in a dry place.

6.5 Nature and contents of container

Type III amber glass bottles closed with an aluminium screw cap with a polyethylene gasket and a polyethylene cover cap.

Aluminium/aluminium strips.

Pack size: 1.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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