SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Idarubicin 1 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 1 mg idarubicin hydrochloride.

Idarubicin hydrochloride 5 mg in a 5 ml vial.
Idarubicin hydrochloride 10 mg in a 10 ml vial.
Idarubicin hydrochloride 20 mg in a 20 ml vial.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear red to orange solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Idarubicin is indicated in adults for the treatment of **acute myelogenous leukaemia**
(also known as acute myeloid leukaemia or **AML**. This type of leukaemia was previously called acute non-lymphoblastic leukaemia or ANLL), for remission induction in untreated patients or for remission induction in relapsed or refractory patients.

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

Idarubicin is indicated in adults and children for the treatment of relapsed **acute lymphoblastic leukaemia** (**ALL**) as second line treatment.

Idarubicin is commonly used in combination chemotherapy regimens involving other cytotoxic agents

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.

Posology

Acute myelogenous leukaemia (AML)
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.

Paediatric population
Combination therapy:
In children with AML the recommended dose range of idarubicin, in combination with cytarabin, is 10-12 mg/m^2 body surface daily for 3 days by slow intravenous injection.

NOTE: These are general guidelines. Refer to individual protocols for exact dosage.

Acute lymphoblastic leukaemia (ALL)
Adults
The suggested dose in adults is 12 mg/m^2 i.v. daily for 3 days in adequate combination regimens.

Paediatric population
10 mg/m^2 i.v. daily for 3 days, in adequate combination regimens.

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 the 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.

A maximum total dose of 120 mg/m² body surface area should not be exceeded.

Patients with hepatic and / or renal impairment:
A dosage adjustment may be required in patients with impaired renal or liver function (see section 4.3, 4.4 and 5.2).

Method of administration

Intravenous administration:
Idarubicin must be administered only by the intravenous route.
The infusion can be prepared by diluting Idarubicin with 0.9% sodium chloride or 5% glucose.
Alternatively the required volume of the undiluted product can be slowly administered over 5 to 10 minutes via the tubing of a freely running intravenous infusion of 0.9% sodium chloride or glucose 5%.
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.

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

4.3 Contraindications

- Hypersensitivity to idarubicin or to any other component of the product, other anthracyclines or anthracenediones
- Severe hepatic impairment
- Severe renal impairment
- Uncontrolled infections
- Severe cardiomyopathy
- Acute inflammatory myocardial disease
- Servere myocardial insufficiency
- Recent myocardial infarction
- Severe arrhythmias
- Persistent myelosuppression
- Previous treatment with maximum cumulative doses of idarubicin and/ or other anthracyclines and anthracenediones (see section 4.4)
- Haemorrhagic diathesis
- stomatitis
- Breastfeeding (see section 4.6)
- Combination with yellow fever vaccine

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.

Systemic infections should be controlled before starting therapy with Idarubicin.

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 i.v. or oral idarubicin have not been defined. However, idarubicin-related cardiomyopathy was reported in 5% of patients who received cumulative i.v. doses of 150 to 290 mg/m2. Available

data on patients treated with oral idarubicin total cumulative doses up to 400 mg/m2 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. 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 elimination half-life of trastuzumab is approximately 28-38 days and subsequently the washout period is up to 27 weeks (190 days or 5 elimination half-lives). Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks 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.

Paediatric population:
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 toxicity of idarubicin and other anthracyclines or anthrachinones is additive.

Haematological toxicity:
Idarubicin is a potent bone marrow suppressant. Severe myelosuppression will occur in all patients given a therapeutic dose of this agent.
Haematological profiles should be assessed before and during each cycle of therapy with idarubicin, including differential white blood cells (WBC) counts.

A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of idarubicin haematologic toxicity and is the most common acute dose limiting 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 hemorrhages 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 preleukaemic 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 events:
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 leukemia 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 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/dl.
With other anthracyclines a 50% dose reduction is generally used if bilirubin levels are in the range of 1,2 – 2,0 mg/dl.

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 minimise the risk of phlebitis/thrombophlebitis at the injection site.

Extravasation:
Extravasation of idarubicin during intravenous injection may cause local pain severe tissue lesions (vesication, severe cellulitis), and right up to necrosis. Should signs or symptoms of extravasation occur during intravenous administration of idarubicin, the drug infusion should be immediately stopped. In cases of extravasation dexrazoxane can be used to prevent or reduce tissue injury.

Tumor Lysis Syndrome:
Idarubicin may induce hyperuricaemia 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 alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumor 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:
Men treated with idarubicin hydrochloride are advised to adopt contraceptive measures during therapy and, 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).

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.
Due to the toxic nature of this substance protective recommendations for health care professionals are given in section 6.6.

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. This 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 leukemia. The clinical significance of this interaction is unknown. A dosage adjustment may be necessary in some patients.

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 up to 3 months after treatment (See section 4.4). Before starting treatment, male patients should be advised to seek counselling on sperm storage. There are no human data on the effect of idarubicin on female fertility. In animals adverse effects of idarubicin have been observed (see section 5.3).

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. Women of childbearing potential should be advised not to become pregnant during treatment and adopt adequate contraceptive measures during therapy as suggested by a physician. 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. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling first if appropriate and available.

Lactation
It is not known whether idarubicin or its metabolites are excreted in human milk. Mothers should not breast-feed during treatment with idarubicin hydrochloride.

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.
However, there is the potential that weak patients might be impaired.

4.8 Undesirable effects

Severe myelosuppression and cardiac toxicity are the two major adverse effects. For further information please refer to section 4.4.

Undesirable effects are similar in adults and children except a greater susceptibility to anthracycline-induced cardiac toxicity of children.

Side effects have been summarised in the table below with MedDRA frequencies.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Organ system	
Frequency	– ***Side effects***
Infection and Infestation:	
Very common	– ***Infection***
Uncommon	– ***Sepsis, Septicaemia***
Neoplasms benign, malignant and unspecified (incl. cysts and polyps:	
Uncommon	– ***Secondary leukaemias (acute myeloid leukaemia and myelodysplastic syndrome)***
Blood and lymphatic system disorders:	
Very common	– ***Anaemia*** – ***Severe leukopenia*** – ***Neutropenia*** – ***Thrombocytopenia*** – ***Pancytopenia***
Immune system disorders:	
Very rare	– ***Anaphylaxis***
Endocrine disorders	
Very common	***Anorexia***
Uncommon	***Dehydration***
Metabolism and nutrition disorders	
Uncommon	– ***Tumour Lysis Syndrome*** – ***Hyperuricaemia***
Nervous system disorders:	
Rare	– ***Cerebral haemorrhage***

Cardiac disorders:	
Common	– ***Congestive heart failure*** – ***Cardiomyopathies ***** – ***Bradycardia*** – ***Sinus tachycardia*** – ***Tachyarrhythmia*** – ***Asymptomatic reductions in left ventricular ejection fraction***
Uncommon	– ***ECG abnormalities**** – ***Myocardial infarction***
Very rare	– ***Myocarditis*** – ***Atrio-ventricular and bundle branch block*** – ***Pericarditis***
Vascular disorders	
Common	– ***Local Phlebitis*** – ***Thrombophlebitis*** – ***Haemorrhage***
Uncommon	– ***Shock***
Very rare	– ***Thromboembolism (including pulmonary embolism*** – ***Flush***
Gastrointestinal disorders:	
Very common	– ***Nausea*** – ***Vomiting*** – ***Mucositis/Stomatitis*** – ***Diarrhoea*** – ***Abdominal pain or burning sensation***
Common	– ***Gastrointestinal tract bleeding, bellyache***
Uncommon	– ***Esophagitis*** – ***Colitis†***
Very rare	– ***Gastric erosions/ulcerations***
Hepatobiliary disorders	
Common	– ***Elevation of liver enzymes and bilirubin***
Skin and subcutaneous tissue disorders	
Very common	– ***Alopecia (usually reversible)***
Common	– ***Rash*** – ***Itch*** – ***Hypersensitivity of irradiated skin ‡***

Uncommon	– ***Skin and nail hyperpigmentation*** – ***Urticaria*** – ***Cellulites§*** – ***tissue necrosis***
Very rare	– ***Acral erythema***
Not known	– ***local reaction***
Renal and urinary tract disorders	
Very common	– ***Red colour to the urine for 1-2 days after treatment***
General disorders and infusion site reactions:	
Very common	– ***Fever*** – ***Headache*** – ***Chills***

* Nonspecific ST segment changes
** See section 4.4 for associated signs and symptoms
† Including severe enterocolitis / neutropenic enterocolitis with perforation
‡ 'Radiation recall reaction'
§ This event can be severe

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 leukaemic 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.

Administration site
Phlebitis/thrombophlebitis and prevention measures discussed in section 4.2; unintended paravenous infiltrates may cause pain, severe cellulites and tissue necrosis.

Other adverse reactions: hyperuricaemia
Prevention of symptoms by hydration, urine alkalinisation, and prophylaxis with allopurinol may minimise potential complications of tumor 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: 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 the anthracyclines up to several months after the overdose.
Patients should be carefully monitored and if signs of cardiac failure arise, they should be treated along conventional lines.

Based on pharmacokinetic parameters neither haemodialysis nor peritoneal dialysis are expected to improve drug elimination.

Suitable facilities to monitor and treat toxicity of the substance in patients should be available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antibiotics; Anthracyclines and related substances

ATC Code: L01DB06

Mechanism of action

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

Idarubicin exhibits antitumour activity against murine leukaemia and lymphomas both by IV and oral routes. In in-vitro studies on human and murine anthracycline-resistant cells idarubicin shows a low degree of cross-resistance.

Pharmacodynamic effects

The modification of position 4 of the anthracycline structure gives the compound 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 IV 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

Distribution
Studies of cellular (nucleated blood and bone marrow cells) distribution of idarubicin in leukaemic patients have shown that peak cellular idarubicin concentrations are reached a few minutes after injection. Due to high lipophilicity, plasma protein binding (97% for idarubicin, 94% for idarubicinol) and distribution in tissues including tumors is extensive. Idarubicin and idarubicinol concentrations in nucleated blood and bone marrow cells are more than a hundred times the plasma concentrations. The volume of distribution amounts to about 1500 l/sqm or, if a mean body surface area of 1.7 sqm and a weight of 70 kg is assumed, to about 13 l /kg.

Metabolisation
Idarubicin is extensively metabolised to its active metabolite idarubicinol by CYP2C9 and CYP2D6 which are present in the liver but also in other tissues.

Elimination
After IV administration to patients with normal renal and hepatic function, idarubicin is eliminated from systemic circulation, the terminal plasma $T_{½}$ ranging between 11 - 25 hours.
The terminal plasma $T_{½}$ of the active metabolite ranges between 41 and 69 hours.
Idarubicin disappearance rates in cells were, with a terminal half-life of about 15 hours, comparable to that of the plasma. The terminal half-life of idarubicinol in cells was about 72 hours.

The drug is eliminated by biliary and renal excretion (less than 10% of the drug and metabolites excreted by the kidneys), mostly in the form of idarubicinol.

Paediatric population:

Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin in doses ranging from 15 to 40 mg/m^2/3 days of treatment, showed a median idarubicin half-life of 8.5 hrs (range: 3.6 – 26.4 hrs). The active metabolite, idarubicinol, accumulated during the 3 days of treatment, exhibiting a median half-life of 43.7 hrs (range: 27.8-131 hrs). In a separate study, pharmacokinetic measurements in 15 paediatric patients receiving oral idarubicin in doses ranging from 30 to 50 mg/m^2/ during the 3 days of Idarubicin treatment, the maximum plasma concentration of idarubicin was 10.6 ng/mL (range 2.7 – 16.7 ng/mL at the 40 mg/m^2 dose). The median terminal half-life of idarubicin of was 9.2 hrs (range: 6.4-25.5 hrs). Significant accumulation of idarubicinol was seen over the 3 day treatment period. The observed terminal half-life value of idarubicin after IV was comparable to that following oral administration in paediatric patients.
In adults, following oral administration of 10 to 60 mg/m^2 idarubicin, idarubicin was rapidly absorbed with the maximum plasma concentrations of 4 - 12.65 ng/mL achieved in 1 to 4 hours after dosing. The terminal half-life was 12.7±6.0 hrs (mean±SD). Following intravenous administration of idarubicin in adults, the terminal half-life was 13.9±5.9 hrs, similar to that observed after the oral administration.
Since cmax of idarubicin is similar in children and adults following oral administrations, absorption kinetics seem not to differ between adults and children.
Following both oral and IV administrations, the elimination half-life values of idarubicin in children and adults differ:
Total body clearance values of 30-107.9 L/h/m^2 for idarubicin reported for adults are higher than the values of 18-33 L/h/m^2 reported for paediatric populations Although idarubicin has a very large volume of distribution in both adults and children, suggesting that much of the drug is bound to tissues, the shorter elimination half-life and lower total body clearance are not entirely explained by a smaller apparent volume of distribution in children compared to adults.

Special populations
Renal or hepatic impairment might lead to increased plasma concentrations of idarubicin.

5.3 Preclinical safety data

Following single IV administration to the mouse, rat and dog, the major target organ was the haematological system and in the case of dogs also the gastro-intestinal system.

During a time period of 13 weeks rats and dogs were administered single intravenous doses at 0.4 mg/kg and 0.3 mg/kg on 3 consecutive days, the target organs were: haemolymphopoetic system (decrease of leukocytes, erythrocytes and related parameters and platelets; atrophy and involution of the spleen and thymus), gastro-intestinal tract (inflammation of the intestine and/or erosions), liver (necrosis, steatosis), kidney (tubular degeneration or atrophy), testis (inhibition of spermatogenesis).

Idarubicin is mutagenic. The substance induces gene and chromosome mutations in a series of test systems.

Idarubicin was teratogenic and embryotoxic in rats, but not in rabbits.

Idarubicin was carcinogenic in rats, even following a single IV dose.

In a local tolerance study on dogs, tissue necrosis resulted after paravasation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol

Hydrochloric acid dilute (for pH-adjustment)

Sodium hydroxide 10% (for pH-adjustment)

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 14 days at 2-8°C and 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Keep the container in the outer carton in order to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Pack of 1 vial, 5 or 10 vials containing 5 ml, 10 ml or 20 ml of sterile solution of idarubicin hydrochloride 1 mg/ml with or without a protective plastic overwrap (ONCO-SAFE).

5 ml clear glass vial (class I) with fluoropolymer coated halobutyl rubber stopper containing 5mg idarubicin hydrochloride.

10 ml clear glass vial (class I) with fluoropolymer coated halobutyl rubber stopper containing 10mg idarubicin hydrochloride.

20 ml clear glass vial (class I) with fluoropolymer coated halobutyl rubber stopper containing 20mg idarubicin hydrochloride.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 Idarubicin should wear protective clothing (e.g. gowns, disposable gloves, safety goggles and a protective mask).
- All handling should take place in a safety cabinet or an isolator.
- The work surface should be covered by an absorptive underpacking with a liquid-leakproof foil for single use.
- All items used for 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 with water. Discolouration shows the loss of cytostatical potency.
- 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.
- Idarubicin is intended for single use only!
- Only clear solutions should be used.
- Before administration the solution should be brought to room temperature.
- Idarubicin shall be prepared not more than 24 hours before administration.
- Mind the risk of bacterial contamination due to manipulation.

Intravenous administration:

Idarubicin must be administered only by the intravenous route.

The infusion can be prepared by diluting Idarubicin with 0.9% sodium chloride or 5% glucose. Alternatively the required volume of the undiluted product can be slowly administered over 5 to 10 minutes via the tubing of a freely running intravenous infusion of 0.9% sodium chloride or glucose 5%.

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.

Disposal:

Remnants of the medicinal product as well as all materials that have been used for reconstitution, for dilution and administration must be destroyed according

to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste.

7 MARKETING AUTHORISATION HOLDER

Sandoz Ltd,
Frimley Business Park,
Frimley, Camberley,
Surrey,
GU16 7SR,
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1602

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/11/2013

10 DATE OF REVISION OF THE TEXT

14/02/2020