DAUNOBLASTINA FOR INJECTION 20 MG
Daunorubicin hydrochloride

1. NAME OF THE MEDICINAL PRODUCT

DAUNOBLASTINA.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains: daunorubicin hydrochloride 20 mg

Excipients with known effect:
Daunoblastina 20 mg/10 mL powder and solvent for solution for injection contains 35.45 mg sodium in each 10 mL solvent ampoule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and Solvent for Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute myeloid leukaemia: Daunoblastina on its own or in association with other antiblastic agents is indicated for the treatment of all stages of this disease. Daunoblastina also has an elective indication in a certain variety of acute leukaemia represented by leukaemia with promyelocytes.

Acute lymphoblastic leukaemia: Daunoblastina is very effective in inducing the remission of this pathological condition but, because of its side effects and the availability of other forms of treatment, its use is essentially indicated only in cases that have been found to be resistant to other drugs.

However, the combined administration of Daunoblastina, prednisone and vincristine has proved to be successful in the initial phase of onslaught of the disease.

Other tumours: Positive results have been observed with Daunoblastina in neuroblastomas and in rhabdomyosarcomas.

Daunoblastina, as part of a combination regimen, is indicated for the treatment of acute lymphocytic leukaemia and acute myeloid leukaemia in children.

4.2 Posology and method of administration

The single dose can vary from 0.5 to 3 mg/kg. The doses of 0.5-1 mg/kg can be repeated at intervals of 1 or more days; the doses of 2 mg/kg should be given at intervals of 4 or

more days; the doses of 2.5-3 mg/kg, although rarely used, should be given only at intervals of 7-14 days.

The number of injections required varies widely from patient to patient and should be prescribed for each individual case, depending on individual response and tolerability, taking into account blood chemistry and bone marrow conditions and any association with other antiblastic agents.

In both adults and children, it is recommended not to exceed the total dose of 20 mg/kg (see section 4.4).

Hepatic impairment
The dosage of Daunoblastina should be reduced in patients who present impairment of liver function to avoid an increase in global toxicity.

It is recommended a dosage reduction in patients with the following chemical parameters in the blood:

Daunorubicin hydrochloride should not be administered to patients with severe hepatic impairment (Child-Pugh Grade C [total score 10-15] - see section 4.3).

For patients with mild and moderate hepatic impairment (Child-Pugh Grade A [total score 5-6] and B [total score 7-9]), dose reductions are recommended based on the following serum bilirubin values:

- Bilirubin 1.2 to 3 mg/dL: one-half of the recommended starting dose.
- Bilirubin >3 mg/dL: one-fourth of the recommended starting dose.

Renal impairment
For patients with moderate renal impairment glomerular filtration rate (GFR) between 10-20 mL/min or serum creatinine approximately between 3.4-7.9 mg/dL, the daunorubicin hydrochloride dose should be reduced by one-half (see section 4.3).

Method of administration
Daunoblastina is not active if taken orally and should not be administered by intramuscular or intrathecal route.

Administration is to be executed only by intravenous injection; it is advisable to execute the injection into the tubing of an intravenous infusion of normal saline solution already in situ, after ascertaining that the needle is perfectly in the vein. This technique reduces the danger of the drug leaking out and ensures that the vein is well washed through after administration of the drug.

Daunoblastina must not be mixed with heparin since these drugs show chemical incompatibility and, in certain proportions, form a precipitate.

Paediatric population
Daunoblastina dosage for paediatric patients (over 2 years of age) is usually calculated based on the body surface area and adjusted to meet individual requirements of each

patient, on the basis of clinical response and the patients' haematological status. Courses may be repeated after 3 to 6 weeks.

Current specialized protocols and guidelines should be consulted for appropriate treatment regimen.

For paediatric patients over 2 years of age the maximum cumulative dose is 300 mg/m^2.

For paediatric patients under 2 years of age (or with body surface area below 0.5 m^2), the maximum cumulative dose is 10 mg/kg.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- hypersensitivity to anthracyclines;
- persistent myelosuppression;
- presence of severe infections;
- severe hepatic (Child-Pugh Grade C (Total score 10-15)) or renal function impairment (GFR <10 mL/min or serum creatinine >7.9 mg/dL);
- myocardial insufficiency;
- recent myocardial infarction;
- severe arrhythmias.

Daunorubicin hydrochloride must not be used if the cumulative highest dose of daunorubicin hydrochloride (500 - 600 mg/m^2 in adults, 300 mg/m^2 in paediatric patients over 2 years of age, 10 mg/kg body weight in paediatric patients under 2 years) or another cardiotoxic anthracycline has already been administered previously, as otherwise the danger of cardiac damage increases markedly.

Women must not breastfeed during treatment.

4.4 Special warnings and precautions for use

When handling daunorubicin hydrochloride all contact with the skin and mucous membranes must be avoided. Increased safety precautions for doctors and nursing staff should be observed because of the potentially mutagenic and carcinogenic action of daunorubicin hydrochloride. Special caution is also advisable for the contact with the patients' excrement and vomit as they may contain daunorubicin hydrochloride or an active metabolite. Pregnant personnel must not be allowed to come into contact with cytostatics.

Relative contraindications are high-grade pancytopenia or isolated leukocytopenia/thrombocytopenia.

Further relative contraindications are severe cardiac arrhythmias in particular ventricular tachycardias or arrhythmias with clinically relevant hemodynamic effects and clinically manifest heart failure – even in the history, myocardial infarction, severe disorders of the kidneys and liver, pregnancy and a poor general condition of the patient. The treating physician weighs benefits and risks and decides in each individual

case on the treatment.

Uncontrolled infections, especially viral diseases (Herpes zoster) can develop into life-threatening exacerbations after daunorubicin hydrochloride administration because of its immunosuppressive effect.

Special caution should be exercised in patients with preceding, concurrent or planned radiotherapy. These patients have an increased risk of local reactions in the radiation area (recall phenomena) during treatment with daunorubicin hydrochloride. A preceding radiation of the mediastinum increases the cardiotoxicity of daunorubicin hydrochloride.

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

Hematopoietic system
After administration of a therapeutic dose, myelosuppression will occur in all patients. Reversible bone marrow suppression develops dose-dependently and consists primarily of leukopenia, granulocytopenia (neutropenia) and thrombocytopenia. Anaemia occurs more rarely. The nadir is achieved 8 to 10 days after starting therapy. Recovery generally occurs 2 to 3 weeks after the last injection.

To avoid myelotoxic complications, careful monitoring of the blood count before and during treatment with special attention to the leukocytes, granulocytes, platelets and erythrocytes is necessary. Fever, infections, sepsis, septic shock, haemorrhages and tissue hypoxia may occur as sequelae of the myelosuppression and these may even lead to death. It must be guaranteed that a severe infection and/or bleeding episode can be treated quickly and effectively. Myelosuppression may require intensive supportive treatment.

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

Cardiotoxicity
Damage to the myocardium is one of the major risks of treatment with daunorubicin hydrochloride.

Toxic myocardial damage by daunorubicin hydrochloride can occur in two forms. The dose-independent “acute type” is manifested by supraventricular arrhythmias (sinus tachycardia, premature ventricular contractions, AV-block) and/or non-specific ECG abnormalities (ST-T wave changes, low voltage QRS complex, T waves). Angina pectoris, myocardial infarction, endomyocardial fibrosis, pericarditis/myocarditis have also been reported. In the “delayed type”, congestive cardiomyopathy may develop, especially after high cumulative doses of daunorubicin hydrochloride. Sometimes this

occurs during therapy, but frequently also only months to years after completing treatment and is clinically manifested by global heart failure, which occasionally leads to death through acute heart failure. The severity and frequency of these side effects depend on the cumulative daunorubicin hydrochloride dose.

Careful monitoring of the cardiac function before, during and after treatment is therefore recommended in order to identify the risk of cardiac complications as early as possible. For routine monitoring the most suitable means are ECG and the determination of the left ventricular ejection fraction (UCG, MUGA scan).

The threshold dose for adults is about 550 mg/m^2, for paediatric patients over two years of age about 300 mg/m^2 and for paediatric patients under 2 years about 10 mg/kg body weight.

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 daunorubicin 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 (variable half-life; washout period up to 7 months), may also be at an increased risk of developing cardiotoxicity. It is therefore recommended to avoid anthracycline-based therapy until the exposure to the previous cardiotoxic agents is negligible. If this is not possible, the patient's cardiac function should be monitored carefully. Under these conditions, a total cumulative dose of 400 mg/m^2 in adults should be exceeded only with extreme caution.

Elderly patients, patients with a history of cardiac disease or manifest arterial hypertension and thoracic irradiation are endangered to a greater degree, as are also children.

Under these conditions, a total cumulative dose of 400 mg/m^2 should not be exceeded in adults. Because of an increased risk of myocardial damage in children and adolescents, long-term cardiologic follow-up observation is recommended in these cases.

Several long-term studies in children also suggest that after anthracycline treatment congestive cardiomyopathies with a latency of many years and a progredient course may occur.

In comparison to adults, already lower cumulative total doses probably lead to clinically relevant cardiac dysfunction. A publication by Steinherz et al. (JAMA, Sep 25, 1991 – Vol 266, no. 12) describes the cardiotoxic long-term side effects of doxorubicin and daunorubicin hydrochloride in 201 treated children. The patients received a cumulative total dose of doxorubicin and /or daunorubicin hydrochloride between 200 and 1275 mg/m^2 (median 450 mg/m^2), partly also mediastinal radiation. Treatments took place 4 to 20 years ago (median 7 years). The cardiotoxicity of doxorubicin was assumed to be comparable to that of daunorubicin hydrochloride.

An impaired cardiac pumping function was seen if the shortening fraction in the echocardiogram was determined to be <29% or the ejection fraction in the radionucleide ventriculogram <50% or a decrease was observed upon physical exercise. The incidence of an impaired cardiac function was 11% when the cumulative anthracycline dose was below 400 mg/m^2, 28% at a dose between 400 mg and 599 mg/m^2 and 47% at a dose between 600 and 799 mg/m^2 and 100% in seven patients who had received more than 800 mg/m^2.

Additional radiation increased the incidence of cardiac dysfunction at each dose stage. 9 out of 201 examined patients additionally experienced cardiac symptoms in the form of cardiac insufficiency, conduction disorders and arrhythmias. In 4 out of the 9 patients affected, symptoms occurred for the first time 12 to 18 years after completion of chemotherapy.

Hepatic impairment
Daunorubicin hydrochloride is metabolized predominantly in the liver and is excreted via the bile. To avoid complications, monitoring of the liver function before starting treatment with daunorubicin hydrochloride is recommended. Impairment of liver function requires a dose reduction, which is based on the serum bilirubin level (see sections 4.2 and 4.3). Patients with serious hepatic impairment must not receive daunorubicin hydrochloride (see section 4.3).

Renal impairment
Impaired renal function can also induce an increase in toxicity. The renal function should therefore be monitored before starting treatment (see sections 4.2 and 4.3).

Hyperuricemia and uric acid nephropathy may occur as a consequence of massive death of the leukemic cells with possible impairment of renal function, especially in the presence of elevated pre-treatment WBC counts. The extent is dependent on the total tumour mass. Prophylactic administration of allopurinol is necessary in the treatment of acute leukaemia (first cycle) in order to avoid tubulous damage with renal failure for the above reasons. The development of a nephrotic syndrome may be induced.

Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricemia may minimise potential complications of tumour-lysis syndrome.

Immunosuppressant Effects/Increased Susceptibility to Infections
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including daunorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving daunorubicin hydrochloride. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Gastrointestinal disorders
Daunorubicin hydrochloride may cause nausea and vomiting. Severe nausea and vomiting may produce dehydration. Nausea and vomiting may be prevented or alleviated by the administration of appropriate antiemetic therapy. Mucositis (mainly stomatitis, more rarely esophagitis) may occur in patients undergoing daunorubicin

hydrochloride therapy. Mucositis/stomatitis generally appear 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.

General disorders and administration site conditions
After paravasal administration local irritation and, depending on the quantity involved, severe cellulitis, painful ulceration and tissue necrosis will occur. Under some circumstances they may require surgical intervention. Irreversible tissue damage is possible. Local phlebitis, thrombophlebitis and/or venous sclerosis/phlebosclerosis may also occur, especially if daunorubicin hydrochloride is injected into small vessels or repeatedly into the same vein. The risk of phlebitis/thrombophlebitis can be minimised by following the procedures recommended (see section 4.2).

Should signs or symptoms of extravasation occur during intravenous administration of daunorubicin hydrochloride, the drug infusion should be immediately stopped.

Skin and subcutaneous tissue disorders
Alopecia. Complete alopecia involving beard growth and the scalp, axillary and pubic hair occurs almost always with full doses of daunorubicin hydrochloride. This side-effect may cause distress to patients but is usually reversible, with regrowth of hair, which usually occurs within two to three months from the termination of therapy.

Reproductive system and breast disorders
Daunorubicin hydrochloride can cause genotoxicity and inhibit fertility. Amenorrhea and azoospermia may occur. The severity is dose dependent. Irreversible disorders of fertility are possible. An effective method of contraception is required for both male and female patients during and for a specified period after completing the treatment with daunorubicin. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available (see sections 4.6 and 5.3).

Neurological disorders

Posterior reversible encephalopathy syndrome (PRES):
Cases of PRES have been reported with daunorubicin used in combination chemotherapy. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with PRES, the discontinuation of daunorubicin treatment should be considered.

Daunoblastina 20 mg/10 mL powder and solvent for solution for injection contains 35.45 mg of sodium in each 10 mL solvent ampoule, equivalent to 1.78% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicinal products and other forms of interactions

As daunorubicin hydrochloride is in most cases used as part of a combination therapy with other cytostatics, total toxicity may be potentiated particularly with regard to myelosuppression and gastrointestinal toxicity. Concurrent use of daunorubicin

hydrochloride and other cardiotoxic substances or a radiation therapy of the mediastinum increase the cardiotoxicity of daunorubicin hydrochloride. Therefore, as with concurrent administration of other cardioactive substances (e.g., calcium antagonists), an especially careful supervision of the heart function during the entire therapy is required. If patients were/are (pre)treated with medicinal products influencing the bone marrow function (e.g., cytostatics, sulphonamides, chloramphenicol, diphenylhydantoin, amidopyrine derivatives, antiretroviral agents) the possibility of a marked disorder of haematopoiesis should be borne in mind. The dose of daunorubicin hydrochloride should be modified if required. If combined with other cytostatics (e.g., cytarabine, cyclophosphamide), the toxic effects of the daunorubicin hydrochloride therapy may be potentiated.

Daunorubicin hydrochloride is mainly metabolized in the liver; each accompanying medication influencing liver function may also influence the metabolism or pharmacokinetics of daunorubicin hydrochloride and as a consequence influence efficacy and/or toxicity. The combination of daunorubicin hydrochloride with potentially hepatotoxic medicinal products (e.g., methotrexate) may upon impairment of the hepatic metabolism and/or biliary excretion of daunorubicin hydrochloride lead to an increase in toxicity of the substance. This may result in a potentiation of the side effects. Upon concurrent administration of other cytostatics, the risk for the incidence of gastrointestinal side effects increases. Medicinal products leading to a delayed excretion of uric acid (e.g., sulphonamides, certain diuretics) may cause potentiated hyperuricemia upon concurrent use of daunorubicin hydrochloride.

It should generally be taken into consideration that the intake and absorption of oral accompanying medicinal products may be considerably influenced by an oral and gastrointestinal mucositis frequently occurring in association with an intensive daunorubicin hydrochloride-containing chemotherapy.

In association with the concurrent intake of thrombocyte aggregation inhibiting substances (e.g., acetylsalicylic acid), an additionally increased bleeding tendency must be anticipated in thrombocytopenic patients.

No vaccinations with viable pathogens should be carried out during daunorubicin hydrochloride therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have shown reproductive toxicity (see section 5.3). Like most other anticancer drugs, daunorubicin has shown embryotoxic, teratogenic, mutagenic and carcinogenic potential in animals.

There are no or limited amount of data from the use of daunorubicin hydrochloride in pregnant women, although a few women who received daunorubicin hydrochloride during the second and third trimesters of pregnancy have delivered apparently normal infants.

According to experimental data, the drug must be considered as a potential cause of foetal malformations when administered to a pregnant woman. Daunorubicin

hydrochloride should not be used during pregnancy unless the clinical condition of the woman requires treatment with daunorubicin hydrochloride and justifies the potential risk to the foetus. Women of child-bearing potential who have to undergo daunorubicin hydrochloride therapy should be apprised of the potential hazard to the foetus and should be advised to avoid becoming pregnant during treatment. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the woman should be informed of the potential hazard to the foetus. The possibility of genetic counselling should also be utilized. In any case, cardiologic examination and a blood count are recommended in foetuses and newborns born to mothers who received treatment with daunorubicin hydrochloride during pregnancy.

Lactation
It is unknown whether daunorubicin hydrochloride or its metabolites are excreted in human milk; other anthracyclines are excreted in breast 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 daunorubicin, breast-feeding is contraindicated (see section 4.3). Women who are breastfeeding should be advised to stop breastfeeding during daunorubicin treatment and for at least 6 days after the last dose.

Fertility
Daunorubicin could induce chromosomal damage in human spermatozoa. Men should receive genetic counselling and be informed on sperm conservation before start of daunorubicin hydrochloride treatment because of the possibility of irreversible infertility.

For women of childbearing age who, after treatment with daunorubicin hydrochloride, wish to become pregnant, genetic counselling and consultation on fertility preservation methods are recommended before starting treatment.

Male and female contraception
Men undergoing treatment with daunorubicin hydrochloride should use effective contraceptive methods during and for at least 14 weeks following the final dose.

Women of childbearing potential have to use effective contraception during treatment with daunorubicin hydrochloride and for at least 27 weeks following the final dose. For women who want to become pregnant after completing daunorubicin hydrochloride treatment, genetic counselling is also recommended.

4.7 Effects on the ability to drive and to use machines

Daunoblastina causes episodes of nausea and vomiting, which sometimes can lead to impairment of the ability to drive or use machines.

4.8 Undesirable effects

The adverse reactions are listed according to MedDRA classification. Frequency categories are defined as: 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).

System Organ Class	Frequency	Undesirable Effects
Infections and Infestations	Very common	Sepsis/septicaemia*; Infections*
	Not known	Septic shock*
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	Uncommon	Acute myeloid leukaemia
	Not known	Myelodysplastic syndrome
Blood and Lymphatic System Disorders	Very common	Anaemia; Granulocytopenia (neutropenia); Leukopenia; Bone marrow failure; Thrombocytopenia
Immune System Disorders	Not known	Anaphylaxis/anaphylactoid reactions
Metabolism and Nutrition Disorders	Not known	Dehydration; Acute hyperuricemia (with possible impairment of renal function especially in the presence of elevated pre-treatment WBC counts)
Cardiac Disorders	Very common	Cardiomyopathy (clinically manifested by dyspnoea, cyanosis, dependent oedema, ascites, pleural effusion and cardiac failure congestive)
	Uncommon	Myocardial infarction
	Not known	Endomyocardial fibrosis; Myocardial ischemia (angina); Pericarditis/myocarditis; Supraventricular tachyarrhythmias
Vascular Disorders	Very common	Haemorrhage
	Not known	Flushes; Shock
Respiratory, Thoracic and Mediastinal Disorders	Not known	Tissue hypoxia
Gastrointestinal Disorders	Very common	Diarrhoea; Oesophagitis; Mucositis/stomatitis; Nausea/Vomiting
	Common	Abdominal pain
	Not known	Colitis
Hepatobiliary Disorders	Not known	Hepatitis; Hepatic failure
Skin and Subcutaneous Tissue Disorders	Very common	Alopecia; Erythema; Skin rash

	Not known	Contact dermatitis; Hypersensitivity to irradiated skin ('radiation recall reaction'); Pruritus; Skin and nail hyperpigmentation; Urticaria
Renal and Urinary Disorders	Not known	Red colour of urine for 1 – 2 days after administration
Reproductive System and Breast Disorders	Not known	Amenorrhea; Azoospermia
General Disorders and Administration Site Conditions	Very common	Fever; Pain
	Common	Local phlebitis
	Not known	Chills; Death; Fulminant hyperpyrexia; Perivenous extravasation; Venous sclerosis; Thrombophlebitis; Phlebosclerosis
Investigations	Very common	Transient elevations in serum bilirubin; Transient elevations in AST; Transient elevations in alkaline phosphatase
	Common	ECG abnormalities

* sometimes fatal.

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.

4.9 Overdose

Overdosage and intoxication
Very high single doses of daunorubicin hydrochloride may cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10 - 14 days.

The occurrence of cardiac damage up to several months after an overdose has been reported for anthracyclines.

Treatment of intoxication
A specific antidote for daunorubicin hydrochloride is not known. In case of myocardial weakness, a cardiologist should be consulted and treatment with daunorubicin hydrochloride withdrawn. In the presence of marked myelosuppression suitable supportive treatment should be initiated, depending on which myelopoietic system is mostly affected, e.g., the transfer of the patient to an aseptic room or transfusion of the lacking cell elements.

Extravasation
Paravenous injection leads to local necroses and thrombophlebitis. Should a burning sensation develop in the region of the infusion needle, this indicates paravenous administration.

Treatment of extravasation
If extravasation occurs, the infusion or injection should be stopped immediately. The needle should initially be left in place and then removed after brief aspiration. It is recommended that dimethyl sulfoxide 99% (DMSO 99%) should be applied locally to an area twice as large as the area affected (4 drops for 10 cm^2 skin surface) and that this should be repeated three times daily over a period of at least 14 days. If necessary, debridement should also be considered. Because of the contradictory mechanism, cooling of the area, e.g., to reduce pain, should take place sequentially with the DMSO application (vasoconstriction versus vasodilatation). Other measures given in literature are disputed and are not of unequivocal value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cytotoxic antibiotics – anthracyclines. ATC code: L01DB02

While it is known that the anthracyclines can interfere with various biochemical and biological functions of the eukaryotic cells, the precise mechanism of the cytotoxic and/or anti-proliferative properties of daunorubicin hydrochloride have not been fully clarified. The drug would appear to inhibit the synthesis of DNA and DNA-dependent RNA through the formation of a molecular complex with the same DNA; or rather the intercalation of the planar rings of the drug between the pairs of nucleotide bases, with unwinding of the helix and impeding of the DNA template activities. Daunorubicin hydrochloride can also interfere with polymerase activity, modifying the regulation of genetic expression, and involve the oxidation reduction reactions with the formation of highly reactive or highly toxic free radicals. The anti-proliferative and cytotoxic activity of daunorubicin hydrochloride could be due to one or more of the above-mentioned mechanisms; and there could also be others. Daunorubicin hydrochloride has its maximum cytotoxicity in the S phase, but it is not a cycle-specific or phase-specific drug.

No controlled paediatric studies have been conducted.

5.2 Pharmacokinetic properties

Absorption
Daunorubicin hydrochloride is not absorbed by the gastrointestinal tract. Since it is extremely irritating for the tissues, it has to be administered by intravenous route: in these conditions absorption is complete.

Distribution
With intravenous administration, daunorubicin hydrochloride is widely distributed within the tissues, with maximum levels in the spleen, kidneys, liver, lungs and heart.

Daunorubicin hydrochloride does not appear to cross the haematoencephalic barrier; while it would appear to cross the placenta.

Metabolism
Daunorubicin hydrochloride is thoroughly metabolised in the liver and in other tissues through the action of cytoplasmic aldo-keto reductases. One hour after administration the predominant species in the plasma is the active metabolite daunorubicinol (13-OH daunorubicin). Further metabolic processes for reductive cleavage of the glycosidic bond produce various aglycones with little or no cytotoxic activity, which are in their turn subject to demethylation and conjugation with sulphate and glycuronate through the action of microsomal enzymes.

Elimination
After administration by rapid intravenous injection, the plasma concentrations of daunorubicin hydrochloride and its metabolites decline in a triphasic manner, while those of the unmodified daunorubicin hydrochloride decline in a biphasic manner. The mean plasmatic half-life of daunorubicin hydrochloride is in the region of 45 minutes for the initial phase and 18 hours for the terminal phase. The terminal half-life of daunorubicinol is more than 24 hours. Daunorubicin hydrochloride and its metabolites are excreted with the urine and in the bile. 40% of the dose is eliminated by biliary excretion. Urinary excretion of the drug and its metabolites varies from 14 to 23% of the dose administered, the greater part in the first three days . After the first 24 hours, the drug is excreted in the urine, mainly as daunorubicinol.

5.3 Pre-clinical safety data

The LD_{50} of daunorubicin hydrochloride has been found to be 17.3-20.0 mg/kg in mice and 13.0-15.0 mg/kg in rats; around 5.0 mg/kg in dogs. The main organs targeted by single doses were found to be the haemolymphopoietic system and (especially in dogs) the gastrointestinal tract. The toxic effects of repeated doses have been studied in rabbits, dogs and monkeys. In these animal species the main targets of the drug were the haemolymphopoietic system, the gastrointestinal tract, the kidneys, the liver and the male and female reproductive organs. As far as the heart is concerned, studies of subacute and cardiac toxicity indicate that daunorubicin hydrochloride is cardiotoxic in all the species examined.

Daunorubicin hydrochloride has been found to be genotoxic in almost all the tests carried out *in vitro* and *in vivo*; the drug has proved toxic for the reproductive organs, embryotoxic in rats and in rabbits and teratogenic in rats. There are no available data on the administration of daunorubicin hydrochloride to animals in the perinatal and postnatal period; nor is it known whether the drug is excreted in the mother's milk. As with other anthracycline compounds and cytotoxic drugs, daunorubicin hydrochloride has proved carcinogenic in rats. In toxicity studies it has been ascertained that perivenous extravasation of the drug causes necrosis of the tissues.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol.

Solvent: normal saline solution.

6.2 Incompatibilities

Daunoblastina must not be mixed with heparin due to the chemical incompatibility which, in certain proportions, can give rise to the formation of a precipitate.

6.3 Shelf life

Please refer to the outer carton for expiry date of unopened vials.

The reconstituted solution remains stable for 24 hours at room temperature, protected from light, and for 48 hours if kept in a refrigerator (2°C-8°C).

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate/freeze.

For the storage conditions after drug reconstitution, see section 6.3.

6.5 Nature and contents of container

Vials made of neutral glass with stopper in butyl rubber.
Ampoule in neutral glass.

6.6 Special precautions for disposal and other handling

The unused medicinal product or waste material should be disposed of in accordance with local requirements.

Pfizer Corporation Hong Kong Limited
SEP 2026

Version approved: 03 NOV 2026