1 NAME OF THE MEDICINAL PRODUCT

Daunorubicin 20mg Powder for I.V. Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 21.4 mg daunorubicin hydrochloride (equivalent to 20 mg as base).
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Vial containing a red lyophilised powder for intravenous administration following reconstitution in Water for Injections and dilution with saline.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Daunorubicin is indicated for the following:
- Inducing remissions of acute myelogenous and lymphocytic leukaemias.
- For the treatment of acute lymphocytic leukaemia and acute myloid leukaemia in children, as part of a combination regimen.

4.2 Posology and method of administration

Adults:40 - 60 mg/m² on alternate days for a course of up to three injections for the induction of remissions.

Acute myelogenous leukaemia:	The recommended dose is 45 mg/m²
Acute lymphocytic leukaemia:	The recommended dose is 45 mg/m²

Paediatric population: Daunorubicin dosage for children (over 2 years) is usually calculated based on the body surface area and adjusted to meet the 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 specialised protocols and guidelines should be consulted for appropriate treatment regimen.

For children over 2 years the maximal cumulative dose is 300 mg/$m^{2.}$

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

Elderly: Daunorubicin should be used with care in patients with inadequate bone marrow reserves due to old age. A reduction of up to 50% in dosage is recommended.

The number of injections required varies widely from patient to patient and must be determined in each case according to response and tolerance.

Daunorubicin should be administered with caution when the neutrophil count is <1,500/mm^3. Daunorubicin dose reduction should be considered in case of severe neutropenia.

The dosage should be reduced in patients with impaired hepatic or renal function. A 25% reduction is recommended in patients with serum bilirubin concentrations of 20 - 50 µmol/l or creatinine of 105 - 265 µmol/l. A 50% reduction is recommended in cases with serum bilirubin concentrations of above 50 µmol/l or creatinine of above 265 µmol/l.

Daunorubicin is extremely irritating to tissues and may only be administered intravenously after dilution. Daunorubicin should be administered through a large vein and the infusion should be kept free flowing. When second or subsequent injections are given, the doses and time intervals depend on the effect of the previous doses and must be the subject of careful deliberation, examination of the peripheral blood and, under some circumstances, of the bone marrow.

The effect of Daunorubicin on the disease process and on normal blood precursors cannot be exactly predicted for any particular case. The difference between incomplete treatment, a satisfactory remission and overdosage with possible irreversible aplasia of the bone marrow depends on the correct choice of dosage, time intervals and total number of doses.

4.3 Contraindications

Hypersensitivity to the active substance, any anthracyclines or to any of the excipients listed in section 6.1.

Daunorubicin should not be used in patients:

- recently exposed to, or with existing, chicken pox or herpes zoster.
- with persistent myelosuppression
- with severe infection
- with severe hepatic or renal function impairment
- with myocardial insufficiency
- having had recent myocardial infarction
- with severe arrhythmias

Do not administer by the intramuscular route.

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 children of 2 years and older, 10mg/kg body weight in children under 2 years) or another cardiotoxic anthracycline has already been previously administered, as otherwise the danger of life-threatening cardiac damage markedly increases.

Women must not breastfeed during treatment.

4.4 Special warnings and precautions for use

Special warnings
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 patients' excrement and vomit as they may contain daunorubicin or an active metabolite. Pregnant personnel must not be allowed to come into contact with cytostatics.

Precautions for use
Daunorubicin should be used under the direction of a clinician conversant with the management of acute leukaemia and cytotoxic chemotherapy. The haematological status of patients should be monitored regularly.

Relative contraindications are high-grade pancytopenia or isolated leuko-/thrombo-cytopenia.

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 should weigh the benefits and risks and decide, 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.

Haematopoietic 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, hemorrhages 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-leukaemic 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/m², for children over two years of age about 300 mg/m² and for children 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, may also be at an increased risk of developing cardiotoxicity. Under these conditions, a total cumulative dose of 400 mg/m2 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/m² 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/m² (median 450 mg/m²), 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/m², 28% at a dose between 400mg and 599mg/m² and 47% at a dose between 600 and 799mg/m² and 100% in seven patients who had received more than 800mg/m². 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 arrthymias. In 4 out of the 9 patients affected, symptoms occurred for the first time 12 to 18 years after completion of chemotherapy.

Liver and renal function

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.

Impaired renal function can also induce an increase in toxicity. The renal function should therefore be monitored before starting treatment.

Daunorubicin should be used with care in patients at risk of hyperuricaemia (e.g. in the presence of gout, urate and renal calculi), tumour cell infiltration of the bone marrow and in patients with inadequate bone marrow reserves due to previous cytotoxic drug or radiation therapy. The cumulative dose of daunorubicin should be limited to 400 mg/m² when radiation therapy to the mediastinum has been previously administered. The dose of daunorubicin should not be repeated in the presence of bone marrow depression or buccal ulceration.

Hyperuricemia and uric acid nephropathy may occur as a consequence of massive death of the leukaemic cells with possible impairment of renal function, especially in the presence of elevated pre-treatment WBC counts. The extent is dependent on the total tumor mass. Prophylactic administration of allopurinol is necessary in the treatment of acute leukaemia (first cycle) in order to avoid tubulus 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 tumor-lysis syndrome.

Immunosuppressant effects/Increased susceptibility to infections

Administration of live or live-attenuated vaccines in patients that are immuno-compromised by chemotherapeutic agents, including daunorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving daunorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Gastrointestinal disorders

Daunorubicin 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/stomatitis 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.

Cases of colitis, enterocolitis and neutropenic enterocolitis (typhlitis) have been observed in patients treated with daunorubicin. Treatment discontinuation and prompt appropriate medical treatment are recommended (see section 4.8).

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 in section 4.2.

Skin and subcutaneous tissue disorders
Complete alopecia involving beard growth and the scalp, axillary and pubic hair occurs almost always with full doses of daunorubicin. 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 inhibits fertility. Amenorrhea and azoospermia may occur. The severity is dose dependent. Irreversible disorders of fertility are possible (see section 4.6).

Care should be taken to avoid extravasation during intravenous administration. All steps should be taken to avoid tissuing and bandages should be avoided. Facial flushing or erythematous streaking along veins indicates too rapid injection. If tissue necrosis is suspected, the infusion should be stopped immediately and resumed in another vein. Where extravasation has occurred, an attempt should be made to aspirate the fluid back through the needle. The affected area may be injected with hydrocortisone. Sodium bicarbonate (5ml of 8.4% w/v solution) may also be injected in the hope that through pH change the drug will hydrolyse. The opinion of a plastic surgeon should be sought as skin grafting may be required.

Application of ice packs may help decrease local discomfort and also prevent extension. Liberal application of corticosteroid cream and dressing the area with sterile gauze should then be carried out.

Infections and infestations
Each patient should be given a clinical and bacteriological examination to determine whether infection is present; any infection should be adequately eliminated before treatment with daunorubicin which might depress the bone marrow to the point where anti-infective agents would no longer be effective. If during daunorubicin treatment a patient becomes febrile (regardless of the neutrophil count), treatment with broad spectrum antibiotics should be initiated. If facilities are available, patients should be treated in a germ-free environment or, where it is not possible, reverse barrier nursing and aseptic precautions should be employed.

Anti-infective therapy should be employed in the presence of suspected or confirmed infection and during a phase of aplasia. It should be continued for some time after the marrow has regenerated. Care should also be used in patients at risk of infection.

Haematology
Daunorubicin can produce bone marrow suppression. Daunorubicin should be administered with caution when the neutrophil count is <1,500/mm^3. Febrile neutropenia has been reported when daunorubicin is given in combination with other antineoplastic treatments.
Monitoring of blood counts prior to and during daunorubicin treatment is recommended, and haematological abnormalities should be treated promptly.

Posterior Reversible Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome, RPLS)

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.

Symptoms, including uncontrolled hypertension, should be treated promptly. Clinical symptoms and MRI changes usually improve within a few weeks after treatment discontinuation. Following resolution of PRES, daunorubicin treatment may be resumed at the discretion of the prescriber. Cases of neurologic sequelae and fatal outcomes have been reported.

Secondary malignancies
Secondary malignancies have been reported when daunorubicin was given in combination with other antineoplastic treatments known to be associated with secondary malignancies. Secondary malignancies (including leukemia) may occur during daunorubicin-containing therapy, or several months or years after the end of therapy. Patients should be monitored for secondary malignancies.

4.5 Interaction with other medicinal products and other forms of interaction

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, sulfonamides, chloramphenicol, diphenylhydantoin, amidopyrine derivatives, antiretroviral agents) the possibility of a marked disorder of hematopoiesis should be borne in mind. The dose of daunorubicin hydrochloride should be modified if

required. If combined with other cytostatics (e. g. cytarabin, 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. sulfonamides, 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

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

Men undergoing treatment with daunorubicin should use effective contraceptive methods during and up to 6 months after treatment.

Women of childbearing potential have to use effective contraception during treatment with daunorubicin. For women who want to become pregnant after completing daunorubicin treatment, genetic counselling is also recommended.

Pregnancy
Daunorubicin crosses the placenta and experiments in animals have shown it to be mutagenic, carcinogenic and teratogenic.

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 in pregnant women, although a few women who received daunorubicin 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 should not be used during pregnancy unless the clinical condition of the woman requires treatment with daunorubicin and justifies the potential risk to the foetus. Women of child-bearing potential who have to undergo daunorubicin 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 during pregnancy.

Breastfeeding
It is unknown whether daunorubicin/metabolites are excreted in human milk; other anthracyclines are excreted in breast milk. Daunorubicin is contraindicated during breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, confusion, seizures and visual disturbances have been observed in patients treated with daunorubicin combination therapy. Therefore, patients should be warned of the possible impact of the side effects on their ability to drive or use machines, and be advised not to drive or use machines if they experience these side effects during treatment.

4.8 Undesirable effects

Blood and the lymphatic system disorders	Bone marrow failure, leucopenia, anaemia, granulocytopenia (neutropenia), thrombocytopenia Frequency not known: febrile neutropenia, including with fatal outcomes, has been reported.
Infections and infestations	*Serious infections (including sepsis, septic shock and pneumonia)
Immune system disorders	Anaphylaxis and anaphylactoid reactions
Metabolism and nutrition disorders	Dehydration, tumor lysis syndrome, acute hyperuricaemia
Nervous system disorders	Frequency not known: Posterior Reversible

	Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome, RPLS), including with fatal outcomes, has been reported.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Secondary malignancies, including leukemia have been reported in association with daunorubicin when used in combination with other antineoplastic treatments known to be associated with secondary malignancies
Cardiac disorders	Cardiomyopathy (clinically manifested by dyspnea, cyanosis, dependent oedema [peripheral, cardiac], hepatomegaly, ascites, pleural effusion and overt congestive heart failure), endomyocardial fibrosis, myocardial ischemia (angina) and myocardial infarction, pericarditis/myocarditis, supraventricular tachyarrhythmias (such as sinus tachycardia, premature ventricular contractions, heart block)
Vascular disorders	Shock, haemorrhage, flushes
Respiratory, thoracic and mediastinal disorders	Tissue hypoxia
Gastrointestinal disorders	Mucositis/stomatitis (pain, or burning sensation, erythema, erosions-ulcerations, bleeding, infections), esophagitis, diarrhoea, nausea, vomiting, abdominal pain, colitis including neutropenic enterocolitis (typhlitis), enterocolitis
Skin and subcutaneous tissue disorders	Alopecia (reversible), contact dermatitis, erythema, hypersensitivity to irradiated skin (‘radiation recall reaction’), pruritus, skin rash, skin and nail hyperpigmentation, urticaria
Renal and urinary disorders	Nephrotic syndrome, uric acid nephropathy, red color of urine for 1 to 2 days after administration
Reproductive system and breast disorders	Amenorrhea, azoospermia
Congenital, familial and genetic disorders	Aplasia
General disorders and administration site conditions	Death, fulminant hyperpyrexia, perivenous extravasation (immediate local pain/burning sensation, severe cellulitis, painful ulceration and tissue necrosis), venous sclerosis/phlebosclerosis, thrombophlebitis, local phlebitis, pain,

	fever, chills
Investigations	ECG abnormalities (such as non-specific ST-T wave changes, low voltage QRS complex, T waves), transient elevations in serum bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase concentrations

***which sometimes can be fatal**

Bone marrow depression
In every patient bone marrow function will be depressed by treatment with daunorubicin and in a variable proportion of cases, severe aplasia will develop. The consequence may include severe infection and opportunistic infection.

Leucopenia is usually more significant than thrombocytopenia. The nadir for leucopenia usually occurs between 10 - 14 days and recovery occurs gradually over the next 1 - 2 weeks. Bone marrow depression must be anticipated in every case by eliminating infection before treatment, by isolating the patient from infection during treatment and by means of supportive therapy. This includes the continuous administration of anti-infective agents, the administration of platelet-rich plasma or fresh whole blood transfusion and, under some circumstances, the transfusion of white cell concentrates.

Rapid destruction of a large number of leukaemia cells may cause a rise in blood uric acid or urea and so it is a wise precaution to check these concentrations three or four times a week during the first week of treatment. Fluids should be administered and allopurinol used in severe cases to prevent the development of hyperuricaemia.

Patients with heart disease should not be treated with this potentially cardiotoxic drug. Cardiotoxicity, if it occurs, is likely to be heralded by either a persistent tachycardia, shortness of breath, swelling of feet and lower limbs or by minor changes in the electrocardiogram and for this reason an electrocardiographic examination should be made at regular intervals during the treatment. Cardiotoxicity usually appears within 1 to 6 months after initiation of therapy. It may develop suddenly and not be detected by routine ECG. It may be irreversible and fatal but responds to treatment if detected early.

The risk of congestive heart failure increases significantly when the total cumulative dosage exceeds 600mg/m² in adults, 300mg/m² in children over 2 years or 10mg/kg in children under 2 years. Cardiotoxicity may be more frequent in children and the elderly. The dosage should be modified if previous or concomitant cardiotoxic drug therapy is used.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

Daunorubicin is an anthracycline glycoside antibiotic and is a potent antileukaemic agent. It also has immunosuppressant effects.

The exact mechanism of antineoplastic action is uncertain but may involve binding to DNA by intercalation between base pairs and inhibition of DNA and RNA synthesis by template disordering and steric obstruction. Daunorubicin is most active in the S-phase of cell division but is not cycle phase specific. Tumour cell cross-resistance has been observed between daunorubicin and doxorubicin.

No controlled paediatric studies have been conducted.

The literature mentions the use of daunorubicin in treatment regimens for ALL and AML, including paediatric age groups. However, due to the ongoing search for a

balance in gain or maintenance of efficacy and a decrease in toxicity the use of daunorubicin in the treatment of paediatric ALL and AML is fluctuating in clinical practice, mainly depending on risk stratification and specific subgroups. Published studies suggest no differences in safety profile between paediatric patients and adults.

5.2 Pharmacokinetic properties

Daunorubicin is rapidly taken up by tissues, especially by the kidneys, spleen, liver and heart. It does not cross the blood-brain barrier, subsequent release of drug and its metabolites from the tissues is slow (t½ = 55 hours). Daunorubicin is rapidly metabolised in the liver. The major metabolite daunorubicinol is also active. Daunorubicin is excreted slowly in the urine, mainly as metabolites with 25% excreted in the first 5 days. Biliary excretion also makes a significant (40%) contribution to elimination.

5.3 Preclinical safety data

No further information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

The reconstituted solution is incompatible with heparin sodium injection and dexamethasone sodium phosphate.

6.3 Shelf life

3 years.
After reconstitution Daunorubicin should be used within 24 hours.

6.4 Special precautions for storage

Store below 25°C and protect from light.
After reconstitution Daunorubicin should be stored at 2 - 8°C, protected from light.

6.5 Nature and contents of container

Glass vial with rubber cap

Pack sizes of 1 vial and 10 vials.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

The contents of a vial should be reconstituted with 4ml of Water for Injection giving a concentration of 5 mg per ml. The calculated dose of Daunorubicin should be further diluted with normal saline to give a final concentration of 1 mg per ml. The solution should be injected over a 20 minute period into the tubing, or side arm, of a well placed, rapidly flowing i.v. infusion of normal saline (to minimise extravasation and possible tissue necrosis). Alternatively, the Daunorubicin may be added to a minibag of sodium chloride injection 0.9% and this solution infused into the side arm of a rapidly flowing infusion of normal saline.

7. MARKETING AUTHORISATION HOLDER

Zentiva Pharma UK Limited
12 New Fetter Lane
London
EC4A 1JP
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 17780/0310

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/04/2005

10 DATE OF REVISION OF THE TEXT

17/03/2020