SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DAUNOBLASTIN® Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg daunorubicin hydrochloride.

Contains sugar alcohol (mannitol).

Excipients with known effect

Each vial contains 100 mg mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

Orange-red freeze-dried cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DAUNOBLASTIN is indicated:

- in the treatment of acute leukaemia
- in the treatment of acute myeloblastic leukaemia as a single medicine or in association with other cytotoxic medicines
- in acute lymphoblastic leukaemia in association with vincristine and prednisone

4.2 Posology and method of administration

Posology

Individual injection may vary from 0,5 - 3 mg/kg. Up to 1 mg/kg may be repeated at intervals of one or more days; doses of 2 mg/kg should be spaced four or more days apart; doses higher than 2,5 mg/kg, if used, should only be given at 7 to 14-day intervals. The dosage is tolerance and response dependant. One injection has sometimes sufficed; normally three to six injections have been necessary and occasionally up to 10 injections in one series have been used.

When second or subsequent injections are to be given, the doses and the 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 marrow.

Total dosage of 20 mg/kg should not be exceeded and consequently DAUNOBLASTIN is not suitable for maintenance therapy.

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

Acute myeloblastic leukaemia

In acute myeloblastic leukaemia each dose should be of about 2 mg/kg, more or less according to effect, repeated at 4 to 7-day intervals. Doses of over 2 mg/kg should be employed with extra caution and at intervals of a week or longer.

Acute lymphoblastic leukaemia

In acute lymphoblastic leukaemia doses of 1 mg/kg may be repeated according to tolerance and effect at 1 to 4-day intervals.

Use in combination with other cytotoxic medicines

When DAUNOBLASTIN is administered together with other cytotoxic medicines which also have a tendency for

marrow depression, dosage should be suitably reduced.

Special populations

Hepatic impairment

DAUNOBLASTIN 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 recommended starting dose;

Bilirubin > 3 mg/mL: one-fourth of recommended starting dose.

Renal impairment

If serum creatinine is above 3,0 mg/dL, the DAUNOBLASTIN dose should be reduced by one-half.

Paediatric population

The dosage of DAUNOBLASTIN is usually based on the patient's body surface area (m^2), but in paediatric patients younger than 2 years of age (or with a body surface area of less than 0,5 m^2) it is suggested to calculate the dosage based on body weight (kg) rather than on body surface area.

For paediatric patients under 2 years of age (or below 0,5 m^2 body surface area), the maximum cumulative dose is 10 mg/kg.

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

For information on cardiac induced toxicity and cardiomyopathy in paediatric patients, refer to section 4.4, Paediatric population.

Method of administration

For intravenous infusion.

Intramuscular, intrathecal and subcutaneous administration should not be used. Severe tissue necrosis will result if administered by the intramuscular or the subcutaneous routes.

DAUNOBLASTIN should be administered only under the supervision of a health care provider who is experienced in the use of cancer chemotherapeutic medicines.

DAUNOBLASTIN is administered by dissolving the calculated dose in 10 - 20 mL of normal saline solution or water for injection and injecting this into the tubing of a fast-running intravenous drip infusion of normal saline solution. This method is used to avoid stasis of the medicine in the vein and to minimise reactions, due to accidental extravasation. It is recommended that the solution is freshly prepared.

4.3 Contraindications

DAUNOBLASTIN is contraindicated in:

- Patients with known hypersensitivity to daunorubicin, other anthracyclines, or anthracenediones or to any other excipient of DAUNOBLASTIN listed in section 6.1
- Patients with persistent myelosuppression, or marked myelosuppression induced by previous treatment with other cytotoxic medicines or radiotherapy
- Patients with impaired cardiac function (including myocardial insufficiency, recent myocardial infarction and severe dysrhythmias)
- Patients who have previously received the full cumulative doses of DAUNOBLASTIN and/or doxorubicin and/or other anthracyclines and/or anthracenediones (see section 4.4)
- Patients with severe infections
- Patients with 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)
- Pregnancy and lactation (see section 4.6).

DAUNOBLASTIN should not be repeated in the presence of buccal ulceration. This condition is sometimes

preceded by a premonitory buccal burning sensation and the repetition of DAUNOBLASTIN therapy in the presence of this symptom is not advised.

4.4 Special warnings and precautions for use

DAUNOBLASTIN is intended for use only by those experienced in the use of cytostatics. The patient must be closely monitored, and electrocardiogram examination should be made regularly to detect signs of cardiotoxicity.

Initial treatment with DAUNOBLASTIN requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalised at least during the first phase of treatment. Blood counts and monitoring of parameters of renal and liver function should be performed prior to each treatment with DAUNOBLASTIN.

Administration of myelosuppressive medicines such as DAUNOBLASTIN may lead to an increased frequency of infections and haemorrhagic complications. These complications are potentially fatal therefore patients should be instructed to notify their health care provider if fever, sore throat, or unusual bruising or bleeding occurs.

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

DAUNOBLASTIN may transiently impart a red discolouration to the urine after administration.

Cardiac toxicity

Special attention must be given (by close cardiac monitoring) to the cardiac toxicity exhibited by DAUNOBLASTIN, especially in infants and children.

DAUNOBLASTIN has a cardiotoxic effect, which can be manifested under two distinct sets of circumstances: Firstly, daily administration of large doses of ≥ 2 mg/kg (or ≥ 55 mg/m^2) will result in transient reversible electrocardiogram (ECG) changes in a proportion of cases. This can be avoided by administering the

medicine at longer intervals.

Secondly, exceeding the total cumulative dose of 20 mg/kg (or 550 mg/m^2) may result in irreversible cardiac failure. This can occur with very little warning and after only a short period of tachycardia.

Cardiomyopathy usually appears within 1 to 6 months after initiation of therapy. It may develop suddenly and may not be detected by routine ECG. It may be irreversible and fatal but responds to treatment if detected early.

Acute and delayed cardiotoxicity

Cardiotoxicity may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early (i.e. acute) events:

Early cardiotoxicity of DAUNOBLASTIN consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, as well as heart 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 consideration for discontinuation of DAUNOBLASTIN treatment.

Late (i.e. delayed) events:

Delayed cardiotoxicity usually develops late in the course of therapy with DAUNOBLASTIN or within 2 to 3 months after treatment termination, but later events (several months to years after completion of treatment) have also been reported.

Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the medicine.

Risk factors for cardiotoxicity

There is increased risk of cardiac toxicity (and lower cumulative dosage limit) in patients previously treated with doxorubicin or in those who received prior or concomitant radiation therapy that encompassed the heart (mediastinal/pericardial area).

Pre-existing active or dormant heart disease, concomitant use of medicines with the ability to suppress cardiac contractility and previous therapy with other anthracyclines or anthracenediones are suspected co-factors of increased risk of DAUNOBLASTIN-induced cardiac toxicity. It is probable that the toxicity of DAUNOBLASTIN and other anthracyclines or anthracenediones is additive.

Anthracyclines including DAUNOBLASTIN should not be administered in combination with other cardiotoxic medicines (e.g. trastuzumab) unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic medicines, 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. Under these conditions, a total cumulative dose of 400 mg/m^2 in adults should be exceeded only with extreme caution.

It has also been suggested, but is not clearly established, that concurrent therapy with cyclophosphamide or some other antineoplastic medicines (e.g. dacarbazine, dactinomycin, mitomycin) may increase the risk of DAUNOBLASTIN-induced cardiotoxicity.

Cardiac function must be carefully monitored in all patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with DAUNOBLASTIN may occur at lower cumulative doses whether or not cardiac risk factors are present.

Total cumulative dosage

The incidence of cardiotoxicity is more frequent in adults receiving a total cumulative dose over 550 mg/m^2 (or over 20 mg/kg body weight) or over 400 mg/m^2 in patients who have received concurrent cyclophosphamide or previous chest irradiation, in the elderly, and in patients with a history of cardiac disease

or mediastinal radiation. In adults, at total cumulative doses less than 550 mg/m^2, acute congestive cardiac failure is seldom encountered, although rare instances of pericarditis-myocarditis, not dose related, have been reported. Also see section 4.4, Paediatric population.

Monitoring of cardiac function

Cardiac function should be assessed before patients undergo treatment with DAUNOBLASTIN and must be monitored throughout therapy to minimise the risk of incurring severe cardiac impairment. There is no absolutely reliable method of predicting the patients in whom acute congestive heart failure will develop as a result of DAUNOBLASTIN therapy. However, certain changes in the ECG and a decrease in the left ventricular ejection fraction (LVEF) from pre-treatment baseline may help to recognise those patients at greatest risk. On the basis of the ECG, a decrease equal to or greater than 30 % in limb lead QRS voltage has been associated with a significant risk of medicine-induced cardiomyopathy. The appropriate quantitative method for repeated evaluation of LVEF includes multi-gated radionuclide angiography (MUGA) 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.

The risk of cardiotoxicity may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of DAUNOBLASTIN at the first sign of impaired cardiac function. Early clinical diagnosis of medicine-induced congestive heart failure appears to be essential for successful treatment with digoxin, diuretics, sodium restriction and bed rest.

Bone marrow depression

Bone marrow depression and consequent marked cytopenia will occur in all patients who receive DAUNOBLASTIN and requires careful monitoring. The severity being dependent on the dose received and the regenerative capacity of the bone marrow. Evaluation of response based on bone marrow status cellularity

is necessary to guide DAUNOBLASTIN treatment.

Myelosuppression is manifested primarily by leukopenia, which is usually severe, and thrombocytopenia. Anaemia may also occur. Leucocyte and platelet nadirs usually occur around days 10 - 14, with recovery around day 21 following therapy.

Haematologic profiles must be carefully assessed before and during each cycle of DAUNOBLASTIN therapy, including differential white blood cell counts.

Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death. During a course of therapy special attention should be devoted to patients with severe neutropenia and fever (febrile neutropenia), a condition that can be possibly followed by septicaemia and death.

In a variable proportion of cases, a severe aplasia will develop which must be anticipated in every case by eliminating infection before treatment, by isolating the patient from infection during the treatment and by the use of supportive therapy, including the continuous administration of anti-infective medicines, the administration of platelet rich plasma or fresh whole blood transfusion and, under some circumstances, the transfusion of blood or white cells from cases of hyper-leukocytic chronic myeloid leukaemia. Therapy with DAUNOBLASTIN should not be started in patients with pre-existing medicine-induced bone marrow depression unless the benefit from such treatment warrants the risk.

Secondary leukaemia

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

Immunosuppression / Increased susceptibility to infections

DAUNOBLASTIN possesses immunosuppressive properties. Appropriate measures should be taken to prevent secondary infection.

Administration of live or live-attenuated vaccines in patients immuno-compromised by chemotherapeutic medicines including DAUNOBLASTIN may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving DAUNOBLASTIN. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished (see section 4.5).

Enhanced toxicity

DAUNOBLASTIN may enhance the toxicity of other cytotoxic medicines when administered concurrently and dosage should be suitably reduced (see section 4.5).

Gastrointestinal effects

Nausea and vomiting are usually mild and transient, occurring soon after administration and lasting 24 to 48 hours. 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, less often oesophagitis) may occur in patients undergoing DAUNOBLASTIN therapy. Mucositis/stomatitis generally appear early after medicine administration (burning and erythema of the oral mucosa; sores in the mouth and/or lips occurring 3 to 7 days after administration) and if severe, may progress over a few days to mucosal ulcerations (7 to 10 days after administration). Most patients recover from this adverse event by the third week of therapy.

Effects at site of injection

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2).

Extravasation

Extravasation of DAUNOBLASTIN at the site of intravenous administration can cause local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of DAUNOBLASTIN, the medicine infusion should be immediately stopped.

Hyperuricaemia / Tumour lysis syndrome

DAUNOBLASTIN may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies rapid medicine-induced destruction of a large number of leukaemia cells (tumour-lysis syndrome).

It is recommended to check the blood uric acid, urea, potassium, calcium phosphate and creatinine levels, three or four times a week during the first week of treatment. Hydration, urine alkalinisation and prophylaxis with allopurinol to prevent hyperuricemia may minimise potential complications of tumour-lysis syndrome.

Neurotoxic effects

There is little evidence of neurotoxic effects.

Alopecia

Complete alopecia involving beard growth and the scalp, axillary and pubic hair occurs almost always with full doses of DAUNOBLASTIN. 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.

Radiotherapy

Adverse effects may be enhanced by radiotherapy. Skin reactions previously induced by radiotherapy may recur.

Increased radiation toxicities such as skin reactions and mucositis may result from concurrent radiotherapy and DAUNOBLASTIN therapy.

Use in hepatic impairment

Hepatotoxic effects have been reported resulting from DAUNOBLASTIN treatment. DAUNOBLASTIN should be used with caution and in reduced doses in the treatment of patients with impaired liver function and the elderly.

The major route of elimination of DAUNOBLASTIN is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with DAUNOBLASTIN. Patients with elevated bilirubin may experience slower clearance of the medicine with an increase in overall toxicity. Lower doses are recommended in these patients (see section 4.2).

Patients with severe hepatic impairment must not receive DAUNOBLASTIN (see section 4.3).

Use in renal impairment

Renal impairment can enhance the toxicity of recommended doses of DAUNOBLASTIN. Prior to administration, it is recommended that renal function be evaluated using conventional clinical laboratory tests. Dosage should be reduced in patients with impaired renal function (see section 4.3 and section 4.2).

DAUNOBLASTIN has been implicated as causing renal failure and should therefore be used with caution when renal damage exists.

Use in the elderly

See section 4.4, Total cumulative dosage for information on incidence of cardiotoxicity in the elderly.

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.

Paediatric patients may be more susceptible to the development of cardiomyopathy than adults. However, the risk of developing cardiomyopathy is reduced with a total dose less than 300 mg/m^2 in paediatric patients over 2 years of age or at a total dosage of less than 10 mg/kg in paediatric patients younger than 2 years of

age with a body surface area of less than 0,5 m^2.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

DAUNOBLASTIN is mainly used in combination with other cytotoxic medicines. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastrointestinal effects (see section 4.4). The use of DAUNOBLASTIN in combination chemotherapy with other potentially cardiotoxic medicines 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 daunorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

Cyclophosphamide

The cardiotoxic effects of DAUNOBLASTIN may be enhanced by concurrent treatment with cyclophosphamide. DAUNOBLASTIN may exacerbate cyclophosphamide induced haemorrhagic cystitis. It is recommended that the total dose of DAUNOBLASTIN not exceed 400 mg/m^2 of body surface area when administered concurrently with cyclophosphamide.

Doxorubicin

Previous treatment with doxorubicin increases the risk of DAUNOBLASTIN induced cardiotoxicity. DAUNOBLASTIN should not be administered to patients who have received the complete cumulative dose of doxorubicin.

Allopurinol, colchicine, probenecid or sulphinpyrazone

DAUNOBLASTIN may raise the concentration of uric acid in the blood. Control of hyperuricaemia and gout may require dosage adjustments to be made for antigout medicines for better control. Allopurinol may be preferred to prevent or reverse DAUNOBLASTIN induced hyperuricaemia because of the risk of uric acid nephropathy with uricosuric antigout medicines.

Other bone marrow depressants

Reduced dosage of DAUNOBLASTIN may be required.

Hepatotoxic medicines

Concurrent administration may increase the risk of hepatotoxicity.

Live virus vaccines

Due to its immunosuppressive properties, concurrent use of DAUNOBLASTIN with a live virus vaccine may potentiate the replication of the vaccine, increase the adverse effects of the vaccine virus, or decrease the patient's antibody response to the virus.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

DAUNOBLASTIN should only be used in women of childbearing potential if the expected benefits outweigh the risks of therapy and adequate contraception is used. If the patient becomes pregnant whilst receiving the medicine, she should be advised of the potential hazard to the foetus.

Women of childbearing potential should use effective contraception during treatment with DAUNOBLASTIN and for at least 27 weeks following the final dose. Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with DAUNOBLASTIN and for at least 14 weeks after the final dose.

Pregnancy

DAUNOBLASTIN should not be used during pregnancy (see section 4.3).

Daunorubicin has shown teratogenic, mutagenic and carcinogenic potential in animals. The medicine must be considered as a potential cause of foetal malformations when administered to a pregnant woman.

Breastfeeding

It is not known whether daunorubicin is excreted in breast milk therefore breastfeeding is not recommended during DAUNOBLASTIN therapy in lactating women. It is recommended that DAUNOBLASTIN is not administered to mothers who are breastfeeding (see section 4.3).

Fertility

DAUNOBLASTIN could induce chromosomal damage in human spermatozoa. Men undergoing treatment with DAUNOBLASTIN should use effective contraceptive methods.

4.7 Effects on ability to drive and use machines

No studies have been assessed with regard to the influence of DAUNOBLASTIN on the ability to drive or use machines. There have been no reports explicitly relating to effects of DAUNOBLASTIN treatment on the ability to drive or use machines. However, DAUNOBLASTIN may cause episodes of nausea and vomiting, which sometimes can indirectly lead to impairment of the ability to drive or use machines. Patients should not drive or use machines before they know how treatment with DAUNOBLASTIN affects their ability to drive and use machines.

4.8 Undesirable effects

The below adverse effects are listed by system organ class and frequency category. 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) (see also section 4.4).

System organ class	Frequency	Adverse effects
Infections and infestations	Very common	Sepsis/septicaemia*, infection*
	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	Bone marrow failure, leukopenia, granulocytopenia, neutropenia, thrombocytopenia, anaemia
Immune system disorders	Not known	Anaphylactic reaction/ anaphylactoid reaction
Metabolism and nutrition disorders	Not known	Dehydration, acute hyperuricaemia[a]
Cardiac disorders	Very common	Cardiomyopathy (clinically manifested by dyspnoea, cyanosis, dependent oedema, hepatomegaly, ascites, pleural effusion and congestive cardiac failure)
	Uncommon	Myocardial infarction
	Not known	Myocardial ischaemia (angina pectoris), endomyocardial fibrosis, pericarditis/

		myocarditis, supraventricular tachydysrhythmias (such as sinus tachycardia, ventricular extrasystoles, atrioventricular block)
Vascular disorders	Very common	Haemorrhage
	Not known	Flushing, shock, thrombophlebitis, phlebosclerosis[b]
Respiratory, thoracic and mediastinal disorders	Not known	Hypoxia
Gastrointestinal disorders	Very common	Nausea/vomiting, diarrhoea, oesophagitis, mucositis/stomatitis[c]
	Common	Abdominal pain
	Not known	Colitis
Skin and subcutaneous tissue disorders	Very common	Alopecia, erythema, rash
	Not known	Contact dermatitis, recall phenomenon, pruritus, skin hyperpigmentation, nail pigmentation, urticaria

Renal and urinary disorders	Not known	Chromaturia[d]
Reproductive system and breast disorders	Not known	Amenorrhoea, azoospermia
General disorders and administration site conditions	Very common	Pyrexia, pain
	Common	Infusion site phlebitis
	Not known	Death, hyperpyrexia, infusion site extravasation[e], chills
Investigations	Very common	Increased blood bilirubin, increased aspartate aminotransferase, increased blood alkaline phosphatase
	Common	Abnormal electrocardiogram, (electrocardiogram ST-T change, abnormal electrocardiogram QRS complex, abnormal electrocardiogram T wave)

* Which can be fatal

[a] With possible impairment of renal function especially in the presence of elevated pre-treatment white blood cell counts.

[b] Venous sclerosis may result from injection of the medicine into a small vessel or from repeated injections into the same vein.

[c] Pain or burning sensation, erythema, ulcer, haemorrhage infection.

[d] Red color of urine for 1 – 2 days after administration.

[e] Infusion site pain/burning sensation, cellulitis, skin ulcer, necrosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms

Clinical features of overdosage are likely to be an extension of DAUNOBLASTIN's pharmacological action. Possible symptoms of toxicity are those listed under section 4.8.

Acute overdosage with DAUNOBLASTIN will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications.

Very high single doses of DAUNOBLASTIN may be expected to cause acute myocardial degeneration (within 24 hours) and severe myelosuppression (within 10 - 14 days).

Management of overdosage

Therapy should be withdrawn should these symptoms occur, and treatment should be symptomatic and supportive. Particular attention should be given to prevention and treatment of possible severe haemorrhages or infections secondary to severe, persistent bone marrow depression.

Delayed cardiac failures have been observed with anthracyclines up to 6 months after an overdose. Patients

have to be observed carefully and if signs of cardiac failure arise, they should be treated along conventional lines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Mechanism of action

Daunorubicin is an antineoplastic antibiotic which is structurally related to doxorubicin. The medicine appears to act by inhibiting DNA and DNA-dependent RNA synthesis by forming a complex with DNA with intercalation between base pairs and uncoiling of the helix. Daunorubicin may also inhibit polymerase activity, affect regulation of gene expression, and be involved in free radical damage to DNA.

Daunorubicin is not cell cycle-phase specific although maximum cytotoxic activity occurs in the S phase. Daunorubicin also has antibacterial and immunosuppressive properties.

5.2 Pharmacokinetic properties

Distribution

Daunorubicin is rapidly and widely distributed in tissues, with highest levels in the heart, kidneys, liver, lungs and spleen. It binds inside the cells to cellular components, mainly nucleic acids.

Daunorubicin does not cross the blood-brain barrier but appears to cross the placenta. It is not known if daunorubicin is present in breast milk.

Metabolism

Daunorubicin is extensively metabolised in the liver and other tissues, mainly by cytoplasmic aldo-keto reductases, producing daunorubicinol, the major metabolite, which has antineoplastic activity. Approximately 40 % of the medicine in the plasma is present as daunorubicinol within 30 minutes and 60 % in 4 hours after a dose of daunorubicin. Additional metabolism by reductive cleavage of the glycosidic bond produces

aglycones, which have little or no cytotoxic activity and are demethylated and conjugated with sulphate and glucuronide by microsomal enzymes.

Daunorubicin metabolism may be altered in patients with impaired hepatic function.

Elimination

Following rapid IV administration, total plasma concentrations of daunorubicin and its metabolites decline in a triphasic manner and plasma concentrations of unchanged daunorubicin decline in a biphasic manner.

The plasma half-life of daunorubicin averages 45 minutes in the initial phase and 18,5 hours in the terminal phase. By 1 hour after administration of daunorubicin, the predominant form of daunorubicin in plasma is the metabolite daunorubicinol, which has an average terminal plasma half-life of 26,7 hours.

Daunorubicin and its metabolites are excreted in the urine and bile, with urinary excretion accounting for 14 - 23 % of the dose. Most urinary excretion of daunorubicin occurs within 3 days. After the first 24 hours, daunorubicin is excreted in urine mainly as daunorubicinol. An estimated 40 % of a dose is eliminated by biliary excretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

Heparin sodium and aluminium are incompatible with DAUNOBLASTIN and will precipitate in solution. Incompatibility has also been reported when DAUNOBLASTIN is mixed with a solution of dexamethasone sodium phosphate, aztreonam, allopurinol sodium, fludarabine and piperacillin/tazobactam. DAUNOBLASTIN can be used in combination with other cytotoxic medicines, but should not be administered mixed with other medicines.

6.3 Shelf life

36 months

Reconstituted solution

Stable for 24 hours when stored at room temperature (at or below 25 °C).

Stable for 48 hours when refrigerated (2 °C - 8 °C).

6.4 Special precautions for storage

Freeze-dried product

Store at or below 25 °C and protect from light.

For the storage conditions of the reconstituted solution, see section 6.3.

6.5 Nature and contents of container

Colourless glass vial containing 20 mg daunorubicin hydrochloride.

6.6 Special precautions for disposal and other handling

Only health care providers, who have been trained in the safe use of the preparation of chemotherapeutic medicines, should prepare DAUNOBLASTIN for administration.

Operations such as transfer to syringes should only be carried out in the designated area. The health care providers carrying out these procedures should be adequately protected with clothing, gloves and eye shields.

Pregnant personnel are advised not to handle cytotoxic medicines.

Where the solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water.

Luer-Lock fitting syringes are recommended.

Spills and disposal

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with absorbent material such as an absorbent towel or adsorbent granules. Spills may also be treated with 3 M sulphuric acid and 0,3 M potassium permanganate (2:1) or 5 % sodium hypochlorite.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27 (0)11) 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

V/26/239

DATE OF FIRST AUTHORISATION

05 December 1988

10. DATE OF REVISION OF THE TEXT

01 March 2024

NAMIBIA: NS2

Reg. No.: 90/26/001305

BOTSWANA: S2

Reg. No.: B9320850

Manufacturer: Corden Pharma Latina S.p.A, Latina, Italy