SCHEDULING STATUS:
S4

PROPRIETARY NAME (and dosage form):
DAUNOBLASTIN® (Injection)

COMPOSITION:
Each vial contains 20 mg Daunorubicin hydrochloride

PHARMACOLOGICAL CLASSIFICATION:
A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:
Daunorubicin is an antineoplastic anthracycline antibiotic produced by Streptomyces coeruleorubidis or S. peucetius. It forms a stable complex with DNA and interferes with the synthesis of nucleic acids.

INDICATIONS:
DAUNOBLASTIN is indicated in the treatment of acute leukaemia.
In the treatment of acute myeloblastic leukaemia as a single agent or in association with other cytotoxic drugs.
DAUNOBLASTIN is also given in acute lymphoblastic leukaemia in association with vincristine and prednisone.

CONTRA-INDICATIONS
In patients with heart disease. It should not be repeated in the presence of bone-marrow depression or of buccal ulceration. The latter condition is sometimes preceded by a premonitary buccal burning sensation and the repetition of DAUNOBLASTIN therapy in the presence of this symptom is not advised. Pregnancy and lactation.

WARNINGS:
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.

DOSAGE AND DIRECTIONS FOR USE:
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 daunorubicin 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.

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.

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

When DAUNOBLASTIN is administered together with other cytotoxic agents which also have a tendency for marrow depression, dosage should be suitably reduced.

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 antibiotic in the vein and to minimise reactions, due to accidental extravasation. It is recommended that the solution is freshly prepared.
Intramuscular and intrathecal administration should not be used.

DAUNOBLASTIN is incompatible with heparin sodium and should not be administered mixed with other drugs.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
Side-effects:
Marrow depression:
In every patient the bone marrow will be depressed by treatment with DAUNOBLASTIN and, in a variable proportion of cases, a severe aplasia will develop.

Cardiotoxic effect:
If a large dose (2 mg/kg or more) is administered at daily intervals, transient reversible tachycardia and ECG changes such as T-wave flattening and S-T depression may occur. Irreversible cardiac failure may be caused but is uncommon below a total dose of 20 mg/kg.

Other:
Subcutaneous extravasation of the drug during intravenous administration will cause a severe local reaction and if the drug is not adequately flushed into the venous system after its introduction, phlebitis may occur.
Gastrointestinal symptoms such as nausea, vomiting or diarrhoea may occur. Alopecia and buccal ulceration may also develop. Thrombophlebitis has been reported following injection.

Special Precautions:
DAUNOBLASTIN should be used with caution and in reduced doses in the treatment of patients with impaired liver function and the elderly.

During treatment with DAUNOBLASTIN haematological monitoring will naturally be routine and attention should be paid to the possibility that bone-marrow depression usually is maximal about ten days after administration.

Adverse effects may be enhanced by radiotherapy and the urine may be coloured red. Skin reactions previously induced by radiotherapy may recur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF TREATMENT:
Acute overdose would be likely to cause the symptoms listed under “SIDE-EFFECTS”. Therapy should be withdrawn should these symptoms occur and treatment should be symptomatic and supportive.

IDENTIFICATION:
Orange-red freeze-dried cake.

PRESENTATION:
Colourless glass vial containing 20 mg daunorubicin hydrochloride.

STORAGE INSTRUCTIONS:
Freeze-dried product:
Store below 25 °C and protect from light.

Reconstituted solution:
Stable for 24 hours when stored at room temperature (25 °C)
Stable for 48 hours when refrigerated (2 °C - 8 °C)

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:
V/26/239

NAME AND BUSINESS ADDRESS OF APPLICANT:
Pfizer Laboratories (Pty) Ltd.
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