SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

Rubexet 10 mg/5 ml (concentrate solution for dilution for IV infusion)

Rubexet 50 mg/25 ml (concentrate solution for dilution for IV infusion)

Rubexet 200 mg/100 ml (concentrate solution for dilution for IV infusion)

COMPOSITION:

Rubexet 10 mg/5 ml: Each vial contains 2 mg of doxorubicin hydrochloride per ml.

Rubexet 50 mg/25 ml: Each vial contains 2 mg of doxorubicin hydrochloride per ml.

Rubexet 200 mg/100 ml: Each vial contains 2 mg of doxorubicin hydrochloride per ml.

The other ingredients are: hydrochloric acid, nitrogen, sodium chloride and water for injection.

PHARMACOLOGICAL CLASSIFICATION:

Category A: 26 - Cytostatics

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

***Mechanism of action*:**

Doxorubicin HCl (hydrochloride) is a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius* and displays broad activity against human neoplasms, including a variety of solid tumours. The exact mechanism of the anti-tumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix, thus preventing their unwinding for replication. Other possible mechanisms of

antineoplastic activity include binding to cell membrane lipids, thus altering a variety of cellular functions and interacting with topoisomerase II to form DNA-cleavable complexes.

Pharmacokinetics:

Distribution:

Doxorubicin HCl is quickly and widely distributed into the extravascular compartments, as indicated by a rapid (5 to 10 min) distribution half-life and by a steady state distribution volume in excess of 20 to 30 litres/kg. Doxorubicin does not cross the blood-brain barrier in detectable amounts but may cross the placenta and is distributed into breast milk. Binding of doxorubicin to plasma protein is extensive.

Metabolism:

Doxorubicin HCl undergoes rapid metabolism in the liver to metabolites including the active metabolite doxorubicinol (adriamycinol). It is eliminated by metabolic conversion to a variety of less active or inactive products.

Excretion:

The elimination half-life of doxorubicin and doxorubicinol is 20 to 48 hours. About 40 to 50 % of a dose is stated to be excreted in bile within 7 days, of which about half is unchanged. Only about 5 % of a dose is excreted in urine within 5 days. Clearance is delayed in the presence of hepatic dysfunction and at least a 50 % initial reduction in dose should be considered in patients with abnormal serum bilirubin levels.

INDICATIONS:

Rubexet is indicated in:

- Acute leukaemias (Acute Lymphoblastic Leukaemia – ALL and Acute Myelogenous Leukaemia – AML), lymphomas and a number of solid tumours
- Metastatic adenocarcinoma of the breast, carcinoma of the bladder, bronchogenic carcinoma and neuroblastoma.

- Metastatic thyroid carcinoma. Carcinoma of the endometrium, testes, prostate, cervix, head and neck and plasma-cell myeloma.
- It is active against carcinoma of the ovary when administered with cisplatin and cyclophosphamide.
- Concurrently with other cytotoxic medicines when administered for carcinoma of the breast and small (oat)-cell carcinoma of the lung.
- Wide range of sarcomas, including osteogenic, Ewing's and soft-tissue sarcoma
- In the ABVD (doxorubicin / bleomycin / vinblastine / dacarbazine) combination it is effective in Hodgkin's disease.
- Concurrently in the BACOP combination in non-Hodgkin's lymphoma

CONTRA-INDICATIONS:

Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones.

Intravenous (IV) use:

- Persistent myelosuppression
- Hepatic impairment
- Myocardial insufficiency
- Recent myocardial infarction
- Severe dysrhythmias
- Previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (See WARNINGS).

Safety in pregnancy and lactation has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

Rubexet should be administered only under the supervision of a doctor experienced in cancer chemotherapy.

Patients should be advised not to conceive and the use of contraceptives are advised.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia,

thrombocytopenia and generalised infections) before beginning treatment with doxorubicin.
Doxorubicin is incompatible with heparin and should also not be mixed with other medicines.
Doxorubicin should be given with great care, in reduced doses, to elderly patients and those with hepatic impairment.
The systemic clearance of doxorubicin is reduced in obese patients (i.e. > 130 % ideal body weight; (See DOSAGE AND DIRECTIONS FOR USE).

Cardiac function:

Initial treatment calls for a careful baseline monitoring of various laboratory parameters and cardiac function.
Severe cardiotoxicity is more likely in adults receiving total cumulative doses greater than 550 mg/m^2 body surface area of doxorubicin, and may occur up to 6 months after administration.
Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early events: This consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachydysrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These events do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for discontinuation of doxorubicin treatment.

Late Events: Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin 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.
Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the

most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the medicine.

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimise the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (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.

Haematologic Toxicity:

Blood counts and measurement of haemoglobin concentration should be carried out routinely. Rubexet may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this medicine. Leukopenia and neutropenia generally reach the nadir between days 10 and 14 after medicine administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death.

Secondary leukaemia:

The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported in patients concurrently treated with Rubexet in association with DNA-damaging antineoplastic agents. Such cases have a short (1-3 year) latency period.

Fertility impairment:

In women, doxorubicin may cause infertility during the time of medicine administration. Doxorubicin may cause amenorrhoea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; Men undergoing doxorubicin treatment should use effective contraceptive methods.

Gastrointestinal:

Doxorubicin is emetogenic. Mucositis/stomatitis generally appears early after medicine 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.

Liver Function:

The major route of elimination of doxorubicin is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with doxorubicin. Patients with elevated bilirubin may experience slower clearance of medicine with an increase in overall toxicity. Lower doses are recommended in these patients (see DOSAGE AND DIRECTIONS FOR USE). Patients with severe hepatic impairment should not receive doxorubicin (see CONTRA-INDICATIONS).

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 minimize the risk of phlebitis/thrombophlebitis at the injection site (see Instructions for use/handling).

Extravasation:

Extravasation of doxorubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during

intravenous administration of doxorubicin, the medicine infusion should be stopped immediately.

Effects on driving and handling machinery:

Due to the frequent occurrence of nausea and vomiting, driving and operation of machinery should be discouraged while on treatment.

INTERACTIONS:

Doxorubicin is mainly used in combination with other cytotoxic medicine. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects (see WARNINGS). The use of doxorubicin in combination chemotherapy with other potentially cardiotoxic medicine, 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 function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

PREGNANCY AND LACTATION:

Rubexet is contra-indicated in:

- Pregnancy and lactation (see CONTRA-INDICATIONS).
- Rubexet crosses the placenta and is distributed into breast milk.

DOSAGE AND DIRECTIONS FOR USE:

Rubexet should not be given orally and should not be injected intramuscularly or subcutaneously. It is administered by intravenous injection.

Intravenous administration:

Intravenous administration of doxorubicin should be performed with caution. It is recommended that the diluted solution of doxorubicin be administered into the tubing of a freely flowing intravenous infusion (isotonic sodium chloride or 5 % glucose solution) over a period of 3 to 5 minutes. This technique is

intended to minimize the risk of thrombosis or perivenous extravasation.

Any unused portion must be discarded as this preparation is intended for single dose administration.

Treatment of solid tumours:

When doxorubicin is administered as a single agent, the recommended dose per cycle is 60-90 mg/ m^2 of body surface area every 3-4 weeks.

Administration of doxorubicin in a weekly regimen of 10-20 mg/m^2 has also been shown to be effective.

The medicine is generally given as a single dose per cycle; however, it is possible to give the medicine dosage per cycle in divided administrations:

- 0,6 mg/kg/day for 3 days (25 mg/m^2 for 3 days) OR
- 0,8 mg/kg/day for 2 days (30 mg/m^2 for 2 days) OR
- 1,6 mg/kg/day for 1 day (60 mg/m^2 for 1 day)

If doxorubicin is used in combination with other antitumour agents, the recommended dose per cycle is in the 30-60 mg/ m^2 range, repeated every 21 days.

As doxorubicin is a myelosuppressive agent, the interval between cycles may need to be increased, or the medicine dosage reduced. In patients whose WBC counts (particularly neutrophils) are below the range of normal values before any treatment cycle. Dosage may also need to be reduced in children.

In the elderly, obese patients and in pre-treated patients in whom the marrow reserve may be low.

Hepatic dysfunction:

In the presence of impaired hepatic function it is suggested that doxorubicin dosage be reduced as follows:

Serum Bilirubin	**Dose reduction**
1,2-3 mg/100 ml	50 % (i.e. 50 % of normal dose to be given

> 3 mg/100 ml	75 % (i.e. 25 % of normal dose to be given

Doxorubicin should not be administered to patients with severe hepatic impairment (see CONTRA-INDICATIONS).

Treatment of acute leukaemias:

In acute leukaemia the dosage schedule is based on the patient's response.

0,4-0,5 mg/kg/day for 3 days is the recommended starting dose. According to the anti-leukaemia and myelosuppressive effect obtained, this course can be repeated a second or even a third time with an interval between courses of not less than 7-10 days.

Incompatibilities:

Doxorubicin should not be mixed with other medicines. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. Doxorubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

INSTRUCTIONS FOR USE/HANDLING RUBEXET:

DO NOT USE MATERIAL THAT SHOWS EVIDENCE OF PRECIPITATION OR ANY OTHER PARTICULATE MATTER.

- Determine the dose to be administered (based upon the recommended dose and the patient's body surface area)
- Take the appropriate volume up into a sterile syringe
- Aseptic techniques must be strictly adhered to since no preservative or bacteriostatic agent is present in this medicine
- The appropriate dose must be diluted in 0,9 % Sodium chloride or Dextrose 5 % in Water prior to administration

- It is recommended that the infusion line of this medicine be connected through the side port of an intravenous infusion of 0,9 % Sodium Chloride or Dextrose 5 % in Water.

Intravenous administration:

Doxorubicin (diluted solution) should be administered into the tubing of a freely flowing intravenous infusion (0,9 % sodium chloride or 5 % glucose solution) for not less than 3-10 minutes to minimize the risk of thrombosis or perivenous extravasation.

A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Protective measures:

The following protective recommendations are given due to the toxic nature of the substance:

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this medicine.
- Personnel handling doxorubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1 % available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

SIDE EFFECTS:

Blood and lymphatic system disorders:

Frequent: Bone marrow depression,

Less frequent: Anaemia, thrombocytopenia, bleeding, immunosuppressant effect.

Immune system disorders:

Less frequent: Hypersensitivity reactions.

Nervous system disorders:

Less frequent: Headache.

Eye disorders:

Less frequent: conjunctivitis, lachrymation

Cardiac disorders:

Less frequent: dysrhythmias, congestive heart failure.

Vascular disorders:

Less frequent: Hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Bronchospasm, radiation pneumonitis.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, stomatitis.

Less frequent: Diarrhoea, oesophagitis, abdominal pain, intestinal ulceration and perforation, buccal ulceration.

Hepato-biliary disorders:

Frequency unknown: Hepatotoxicity, transient increase of liver enzymes.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, facial flushing.

Renal and urinary disorders:

Less frequent: Urine discolouration, hyperuricaemia, acute renal failure, nephrotoxicity, hyperphosphataemia.

Reproductive system and breast disorders:

Less frequent: Amenorrhoea, inhibition of spermatogenesis, gynaecomastia.

General disorders and administrative site conditions:

Less frequent: Fever, malaise, weakness.

Frequency unknown: Thrombophlebitis, streaking of the skin, extravasation.

Investigations:

Frequency unknown: ECG abnormalities.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Acute overdosage may cause gastrointestinal symptoms, buccal ulceration and bone marrow depression. Should these symptoms occur therapy should be stopped.

A cumulative dosage above 500 mg/m^2 may cause irreversible cardiac failure. Treatment is supportive and symptomatic.

IDENTIFICATION:

Rubexet 10 mg/5 ml: A clear red solution, filled in clear glass vial when examined under suitable conditions of visibility it should be free from particles.

Rubexet 50 mg/25 ml: A clear red solution, filled in clear glass vial. When examined under suitable conditions of visibility it should be free from particles

Rubexet 200 mg/100 ml: A clear red solution, filled in a clear glass vial. When examined under suitable conditions of visibility it should be free from particles.

PRESENTATION:

Rubexet 10 mg/5 ml: concentrate solution for dilution for IV infusion is packaged in a 5 ml type I transparent clear glass vial, with a 20 mm teflon rubber stopper and a 20 mm aluminium flip-off pink seal.

Rubexet 50 mg/25 ml: concentrate solution for dilution for IV infusion is packaged in a 30 ml type I transparent clear glass vial, with a 20 mm teflon rubber stopper and a 20 mm aluminium flip-off pink seal.

Rubexet 200 mg/100 ml: concentrate solution for dilution for IV infusion is packaged in a 100 ml type I clear glass vial, with a 20 mm teflon rubber stopper and a 20 mm aluminium flip-off pink seal.

STORAGE INSTRUCTIONS:

Store at or below 2-8 °C.

Keep tightly closed.

Protect from light.

Keep out of reach of children.

Store in unit carton until required for use.

Do not freeze

Infusion preparation:

The medicinal product is for single use only. Any unused solution should be discarded.

After dilution with 0,9 % Sodium Chloride or Dextrose 5 % in water the diluted solution should be used immediately.

REGISTRATION NUMBER:

Rubexet 10 mg/5 ml: 46/26/0487

Rubexet 50 mg/25 ml: 46/26/0488

Rubexet 200 mg/100 ml: 46/26/0489

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

2 October 2014