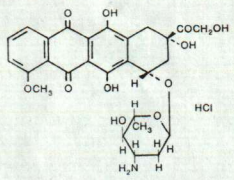
FARMORUBICIN RAPID DISSOLUTION

epirubicin

DESCRIPTION - Farmorubicin (epirubicin hydrochloride) is a new anthracycline antibiotic with antiblastic activity, synthesised in the Farmitalia Carlo Erba Research laboratories. Its structural formula is as follows:



BIOLOGICAL ACTIVITY - The mechanism of action of Farmorubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Farmorubicin has proved to be active on a wide spectrum of experimental tumours including L 1210 and P 388 leukemias, sarcomas SA 180 (solid and ascitic forms), melanoma B 16, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).
Toxicity studies in animals have indicated that Farmorubicin has a better therapeutic index and less systemic and cardiac toxicity than doxorubicin.

CLINICAL PHARMACOLOGY - In patients with normal hepatic and renal function, plasma levels after i.v. injection of 75-90 mg/m² of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours.
Plasma levels of the drug's main metabolite, the 13-OH derivative, are constantly lower and virtually parallel those of the unchanged drug. Farmorubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. The drug does not cross the blood-brain barrier.

INDICATIONS - Farmorubicin has produced responses in a wide spectrum of neoplastic diseases including: breast carcinoma; malignant lymphomas; soft-tissue sarcoma; gastric, hepatic, pancreatic and sigma-rectum carcinomas; head and neck carcinoma; lung carcinoma; ovarian carcinoma and leukemias.

CONTRAINDICATIONS - Farmorubicin is contraindicated in patients with marked myelosuppression induced by previous treatments with other antitumour agents or by radio-therapy, and in patients already treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin.
The drug is contraindicated in patients with a current or previous history of cardiac impairment.
Hypersensitivity to hydroxybenzoates is a controindication.

DOSAGE - When Farmorubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body area; the drug should be injected i.v. over 3-5 minutes and, depending on the patient's haematomedullar status, the dose should be repeated at 21-day intervals.
Lower doses (60-75 mg/m²) are recommended for patients whose bone marrow function has already been impaired by previous chemotherapy or radio-therapy, by age, or neoplastic bone-marrow infiltration.
The total dose per cycle may be divided over 2-3 successive days. When the drug is used in combination with other antitumour agents, the doses need to be adequately reduced. Since the major route of elimination of Farmorubicin is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. Moderate liver impairment (bilirubin: 1.4-3 mg/100 ml, or BSP retention: 9-15%) requires a 50% reduction of dose while severe impairment (bilirubin > 3 mg/100 ml or BSP retention > 15%) necessitates a dose reduction of 75%.
Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Farmorubicin excreted by this route.

PRECAUTIONS - During the first cycles of treatment with Farmorubicin patients must be carefully and frequently monitored.
White and red blood cells and platelet counts should be carefully monitored. Leukopenia is usually transient with normal dosage schedules, reaching a nadir between the 10th and 14th day, but returning to normal values by the 21st day.
Before starting therapy and if possible during treatment, liver function should be evaluated (SGOT, SGPT, alkaline phosphatase, bilirubin, BSP).
Experimental animal data and results of short-term trials in man indicate that Farmorubicin is less cardiotoxic than its structural analogue, doxorubicin.
It has been shown, in a comparative study, that the ratio of cumulative doses, which lead to the same reduction in cardiac function, is of the order of 2:1. In addition, in patients previously untreated with doxorubicin, congestive heart failure has only been reported after cumulative doses exceeding 1000 mg/m².
However, cardiac function must be carefully monitored during treatment to minimize the risk of heart failure of the type described for other anthracyclines.

This heart failure can appear even several weeks after discontinuing treatment, and may prove unresponsive to specific medical treatment.
The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radio-therapy to the mediastinal pericardial area. In establishing the maximal cumulative doses of Farmorubicin any concomitant therapy with potentially cardiotoxic drugs should be taken into account.
It is recommended that an ECG before and after each treatment cycle should be carried out. Alterations in the ECG tracing, such as flattening or inversion of the T wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment.
Cardiomyopathy induced by anthracyclines, and by doxorubicin in particular, is associated with a persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction.
Cardiac monitoring of patients receiving Farmorubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques such as ECG, echocardiography and, if necessary, measurement of ejection fraction by radionuclide angiography. Like other cytotoxic agents, Farmorubicin may induce hyperuricemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be carefully checked so that this phenomenon may be controlled pharmacologically.
To date there is no conclusive information as to whether this drug may adversely affect human fertility, or cause teratogenic or other harmful effects to the foetus; experimental data, however, suggest that Farmorubicin may reduce foetal viability. Its use in pregnancy is therefore not recommended.
Like most other antitumoral and immunosuppressant agents, Farmorubicin, under particular experimental conditions, has mutagenic properties and is carcinogenic in laboratory animals.
Farmorubicin may impart a red colour to the urine for 1-2 days after administration.

ADVERSE REACTIONS - Apart from myelosuppression and cardiotoxicity (described under Precautions) the following adverse reactions have been described:
- alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males;
- mucositis may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, mainly along the sides of the tongue and on the sublingual mucosa;
- gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea;
- hyperpyrexia.

DIRECTIONS FOR ADMINISTRATION - Farmorubicin Rapid Dissolution should be administered by intravenous injection.
It is not active when given orally and should not be injected intramuscularly or intrathecally.
It is advisable to give the drug via the tubing of a freely- running i.v. saline infusion after checking that the needle is well placed in the vein. This method minimizes the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of Farmorubicin Rapid Dissolution from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.
Farmorubicin Rapid Dissolution should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.
Farmorubicin Rapid Dissolution can be used in combination with other antitumour agents, but it is not recommended that it be mixed with these drugs in the same syringe.

PREPARATION OF THE SOLUTION - Farmorubicin Rapid Dissolution should be dissolved in sterile water for injection as indicated in the table below:

Freeze-dried vial	Diluent added	Final concentration
10 mg	5 ml	2 mg/ml
50 mg	25 ml	2 mg/ml

After adding the sterile water, shake the vial until the drug has completely dissolved. The reconstituted solution is stable for 24 hours at room temperature, and for 48 hours in a refrigerator (4-10° C). It should be protected from light.
It is advisable that personnel handling this drug should wear protective gloves. Accidental contact of Farmorubicin powder or solution with skin or mucosae should be treated immediately by copious lavage with soap and water. The conjunctiva should be washed with saline solution.

WARNINGS - Farmorubicin Rapid Dissolution should be administered only under the supervision of qualified physicians experienced in antiblastic ans cytotoxic therapy.
Initial treatment calls for a careful baseline monitoring of various laboratory parameters and cardiac function.

PRESENTATIONS - Farmorubicin hydrochloride is supplied as:
- 10 mg vials containing 10 mg of epirubicin hydrochloride as a freeze- dried powder, with a solvent ampoule containing 5 ml of water for injection.
- 50 mg vials - containing 50 mg of epirubicin hydrochloride as a freeze- dried powder.