Rubitor™

Epirubicin Hydrochloride for Injection

DESCRIPTION

Rubitor™ is a preparation of Epirubicin hydrochloride. Epirubicin is an anthracycline cytotoxic agent. Although it is known that anthracyclines can interfere with a number of biochemical and biological functions within eukaryotic cells, the precise mechanisms of Epirubicin's cytotoxic and/or antiproliferative properties have not been completely elucidated. Epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis. Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Epirubicin also inhibits DNA helicase activity, preventing the enzymatic separation of double-stranded DNA and interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and cytotoxic activity of Epirubicin is thought to result from these or other possible mechanisms.

INDICATIONS

Rubitor™ is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

DOSAGE AND ADMINISTRATION

Epirubicin hydrochloride for injection is administered to patients by intravenous infusion. It is given in repeated 3- to 4-week cycles. The total dose of Epirubicin hydrochloride for injection may be given on Day 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle. The recommended dosages of Epirubicin hydrochloride for injection are as follows:

Starting Doses:

The recommended starting dose of Epirubicin hydrochloride for injection is 100 to 120 mg/m^2. The following regimens were used in the trials supporting use of Epirubicin hydrochloride for injection as a component of adjuvant therapy in patients with axillary-node positive breast cancer:

CEF-120:

- Cyclophosphamide: 75 mg/m^2 PO D 1-14
- Epirubicin Hydrochloride for Injection: 60 mg/m^2 IV D 1, 8
- 5-Fluorouracil: 500 mg/m^2 IV D 1, 8
- Repeated every 28 days for 6 cycles

FEC-100:

- 5-Fluorouracil: 500 mg/m^2
- Epirubicin Hydrochloride for Injection: 100 mg/m^2
- Cyclophosphamide: 500 mg/m^2
- All drugs administered intravenously on Day 1 and repeated every 21 days for 6 cycles

Patients administered the 120 mg/m^2 regimen of Epirubicin hydrochloride for injection also received prophylactic antibiotic therapy.

Bone Marrow Dysfunction:

Consideration should be given to administration of lower starting doses (75 to 90 mg/m^2) for heavily pretreated patients, patients with pre-existing bone marrow depression, or in the presence of neoplastic bone marrow infiltration.

Dose Modifications:

Dosage adjustments after the first treatment cycle should be made based on hematologic and nonhematologic toxicities. Patients experiencing during treatment cycle nadir platelet counts <50,000/mm^3, absolute neutrophil counts (ANC) <250/mm^3, neutropenic fever, or Grades 3/4 nonhematologic toxicity should have the Day 1 dose in subsequent cycles reduced to 75% of the Day 1 dose given in the current cycle. Day 1 chemotherapy in subsequent courses of treatment should be delayed until platelet counts are ≥ 100,000/mm^3, ANC ≥ 1500/mm^3, and nonhematologic toxicities have recovered to ≤ Grade 1. For patients receiving a divided dose of Epirubicin hydrochloride for injection (Day 1 and Day 8), the Day 8 dose should be 75% of Day 1 if platelet counts are 75,000 to 100,000/mm^3 and ANC is 1000 to 1499/mm^3. If Day 8 platelet counts are <75,000/mm^3, ANC <1000/mm^3, or Grade 3/4 nonhematologic toxicity has occurred, the Day 8 dose should be omitted.

INCOMPATIBILITIES

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. Epirubicin Hydrochloride for Injection should not be mixed with heparin or fluorouracil due to chemical incompatibility that may lead to precipitation. Epirubicin Hydrochloride for Injection can be used in combination with other antitumor agents, but it is not recommended that it be mixed with other drugs in the same syringe.

PREPARATION OF INFUSION SOLUTION

Reconstitution:

Prior to use, Epirubicin hydrochloride for injection 10 mg and 50 mg vials must be reconstituted with 5 mL and 25 mL, respectively, of Sterile Water for Injection, USP, resulting in a solution concentration of 2 mg/mL. Shake vigorously. It may take up to 4 minutes for Epirubicin Hydrochloride to completely dissolve. Reconstituted solutions are stable for 24 hours when stored at 2 to 8 °C (36 to 46 °F) and protected from light or 25 °C (77 °F) in normal lighting conditions. Epirubicin hydrochloride for injection can be further diluted with Sterile Water for Injection, USP.

Administration:

Epirubicin hydrochloride for injection should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose solution). Patients receiving initial therapy at the recommended starting doses of 100 to 120 mg/m^2 should generally have Epirubicin infused over 15 to 20 minutes. For patients who require lower Epirubicin starting doses due to organ dysfunction or who require modification of Epirubicin doses during therapy, the Epirubicin infusion time may be proportionally decreased, but should not be less than 3 minutes. This technique is intended to minimize the risk of thrombosis or perivenous extravasation, which could lead to severe cellulitis, vesication, or tissue necrosis. 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. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein. Epirubicin hydrochloride for injection should be used within 24 hours of first penetration of the rubber stopper. Discard any unused solution.

DRUG INTERACTIONS

1. Epirubicin hydrochloride for injection when used in combination with other cytotoxic drugs may show on-treatment additive toxicity, especially hematologic and gastrointestinal effects.
2. Concomitant use of Epirubicin hydrochloride for injection with other cardioactive compounds that could cause heart failure (e.g., calcium channel blockers), requires close monitoring of cardiac function throughout treatment.
3. Epirubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect Epirubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.
4. Cimetidine increased the AUC of Epirubicin by 50%. Cimetidine treatment should be stopped during treatment with Epirubicin hydrochloride for injection.

CONTRAINDICATIONS

- Hypersensitivity
- Baseline neutrophil count <1500 cells/mm^3
- Severe myocardial insufficiency
- Recent myocardial infarction
- Severe arrhythmias

OVERDOSAGE

If an overdose occurs, supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony-stimulating factors, and intensive care as needed) should be provided until the recovery of toxicities. Delayed CHF has been observed months after anthracycline administration. Patients must be observed carefully over time for signs of CHF and provided with appropriate supportive therapy.

ADVERSE REACTIONS

- Hematologic: Leukopenia, neutropenia, anemia, thrombocytopenia
- Endocrine: Amenorrhea, hot flashes
- Body as a whole: Lethargy, fever
- Gastrointestinal: Nausea/vomiting, mucositis, diarrhea, anorexia
- Skin: Alopecia, local toxicity, rash/itch, skin changes
- Infection: Infection, Febrile Neutropenia
- Ocular: Conjunctivitis, Keratitis

WARNING AND PRECAUTION

1. Severe local tissue necrosis will occur if there is extravasation during administration. Epirubicin must not be given by the intramuscular or subcutaneous route.
2. Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with Epirubicin or months to years after termination of therapy.
3. Cardiac toxicity with Epirubicin hydrochloride for injection may occur at lower cumulative doses whether or not cardiac risk factors are present.
4. Secondary Acute Myelogenous Leukemia (AML) has been reported in patients with breast cancer treated with anthracyclines, including Epirubicin.
5. Epirubicin hydrochloride for injection is administered by intravenous infusion. Venous sclerosis may result from an injection into a small vessel or from repeated injections into the same vein.
6. Extravasation of Epirubicin during the infusion may cause local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. It is recommended that Epirubicin hydrochloride for injection be slowly administered into the tubing of a freely running intravenous infusion.
7. Dosage should be reduced in patients with impaired hepatic function.
8. Severe myelosuppression may occur.

PRECAUTIONS FOR HANDLING AND DISPOSAL

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Procedures normally used for proper handling and disposal of anticancer drugs should be considered for use with Epirubicin hydrochloride for injection.

Protective Measures:

The following protective measures should be taken when handling Epirubicin hydrochloride for injection.

- Epirubicin hydrochloride for injection is to be used under medical supervision. Personnel should be trained in appropriate techniques for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling Epirubicin hydrochloride for injection should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for syringe preparation (preferably under a laminar flow system), with the work surface 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 contaminated and cleaning materials should be placed in high-risk, waste-disposal bags for incineration. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Medical attention should be sought. Always wash hands after removing gloves.

USE IN PREGNANCY AND LACTATION

Pregnancy category D. Epirubicin was excreted into the milk of rats treated with 0.50 mg/kg/day of Epirubicin during peri- and postnatal periods. It is not known whether Epirubicin is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Epirubicin, mothers should discontinue nursing prior to taking this drug.

PHARMACEUTICAL PRECAUTION

Store at or below 30 °C temperature. Keep away from light and wet place. Keep out of reach of children.

PACKAGING

Rubitor™ 10 for IV Injection: Each box contains 1 vial of Epirubicin Hydrochloride BP 10 mg (as lyophilized powder).

Rubitor™ 50 for IV Injection: Each box contains 1 vial of Epirubicin Hydrochloride BP 50 mg (as lyophilized powder).

SK+F ONCOLOGY

Manufactured by
ESKAYEF PHARMACEUTICALS LIMITED
RUPGANJ, NARAYANGANJ, BANGLADESH
TM TRADEMARK
R/PM0860 V01