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CANCER TREATMENTS

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Epirubicin Hydrochloride

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Drug name: Epirubicin hydrochloride is manufactured as Ellence[®] (Pharmacia and Upjohn Company, Peapack, NJ).

Classification: Anthracycline antibiotic analogue

Action: Epirubicin is a semisynthetic derivative of daunorubicin and the 4'-epimer of doxorubicin. Its action is unclear; it forms a complex with DNA, causing inhibition of nucleic acid and protein synthesis. The drug appears to interfere with replication and transcription of DNA, leading to cell death.

Indication: Epirubicin is approved for adjuvant breast cancer treatment in node positive, resectable primary breast cancer. Currently, clinical trials evaluating its use in metastatic breast cancer and other cancers (e.g., gastric, lung, liver) are ongoing. Although the U.S. Food and Drug Administration (FDA) recently approved epirubicin in the United States, the drug has been used extensively in Europe.

Metabolism: Liver **Excretion:** Biliary and renal **Half-life:** 30–35 hours

Effect on blood counts: Epirubicin caused grades 1-4 neutropenia in 80% of patients in clinical trials, with approximately 67% being grades 3-4. The white blood cell nadir is reached 10-14 days after administration and is usually transient, with normal bone marrow recovery in 21-28 days. Treatment should be delayed until the absolute neutrophil count (ANC) is greater than 1,500/ mm3. Neutropenia or leukopenia can occur and lead to fever, infection, or sepsis. Appropriate supportive measures should be considered, such as colony-stimulating factors. Anemia (grades 1-4) was reported in approximately 72% of patients in clinical trials, although less than 6% were grades 3-4. Thrombocytopenia occurred in approximately 48% of patients, although it rarely develops into grades 3-4.

Adverse reactions and effects: The primary dose-limiting side effect is hematologic toxicity, which may require colonystimulating factors to avoid treatment delays and dose reductions. Gastrointestinal toxicity also can occur and includes nausea, vomiting, and mucositis and stomatitis. Epirubicin is emetogenic; patients should receive a 5HT₃ antagonist with or without dexamethasone prior to treatment. Patients should be provided with oral antiemetic prescriptions for use at home. Grades 1–4 mucositis occurred in approximately 58% of patients in clinical trials. Mucositis can be a severe dose-limiting toxicity. Supportive measures, such as mucositis mouth solutions (e.g., diphenhydramine, lidocaine, other agents), chlorhexidine gluconate oral rinse, and proper oral hygiene, should be recommended.

Other toxicities include amenorrhea, which occurred in 72% of patients in clinical trials. Amenorrhea may be permanent and cause premature menopause, depending on the patient's age. Hot flashes were reported in up to 40% of patients. Alopecia occurs and is transient. Radiation recall is associated with epirubicin administration. Hypersensitivity reactions also have been reported. Although rare, they may vary from a skin rash to fever, chills, and shock.

Delayed toxicities include cardiac dysfunction and development of leukemia. Cardiac effects include change in the left ventricular ejection fraction (LVEF) and the development of congestive heart failure (CHF). A cumulative dose of 900 mg/m² should only be exceeded with extreme caution and close monitoring of cardiac function, which should include periodic physical exams and multiplegated acquisition scanning or echocardiogram to evaluate LVEF. In clinical trials, 1.8% of patients were noted to have an asymptomatic decrease in LVEF and 1.5% developed CHF. Acute myelogenous leukemia occurred in 0.8% of patients in clinical trials.

Route: Epirubicin is administered via IV. **Dosage:** Two regimens have been FDA approved for adjuvant breast cancer treatment. The recommended starting dose of epirubicin is 100–120 mg/m². The first regimen is the protocol CEF-120, which consists of cyclophosphamide 75 mg/m² orally d1– 14, epirubicin 60 mg/m² IV d1 and d8, and 5-fluorouracil (5-FU) 500 mg/m² IV d1 and d8, repeated every 28 days for six cycles. The second regimen is FEC-100, which consists of 5-FU 500 mg/m² IV d1, epirubicin 100 mg/m² IV d1, and cyclophosphamide 500 mg/m² IV d1, repeated every 21 days for six cycles. Patients who receive the CEF proto-

col are recommended to receive prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole or a fluoroquinolone. Assessment of bone marrow function should be evaluated prior to each cycle. Dose delays should be considered if platelet counts are below 100,000/mm³ or ANC is less than 1,500/mm³. Supportive measures, such as colony-stimulating factors, should be considered, or dose reductions if the cycle nadir platelet count is less than 50,000/mm3, ANC is less than 250/mm3, or neutropenic fever develops. Hepatic function also should be assessed, and if bilirubin is 1.2-3 mg/dl or aspartate aminotransferase (AST) is two to four times the upper limit of normal, one-half of the recommended starting dose should be considered. If bilirubin is 3 mg/dl or AST is more than four times the upper limit of normal, one-fourth of the recommended starting dose is advised.

Dilution and reconstitution: Epirubicin is available in 2 mg/ml, single-use vials in strengths of 50 mg/25 ml and 200 mg/100 ml.

Interactions: Epirubicin may cause severe myelosuppression, and patients should be monitored closely. Epirubicin used with other cytotoxic medications may cause increased effects of toxicities (e.g., hematologic, gastrointestinal) and should be monitored closely and receive preventive, supportive management. The concomitant use of calcium channel blockers and epirubicin requires close monitoring of cardiac function during treatment. Cimetidine increases the mean area under the curve of epirubicin by 50% and should be discontinued while the patient is receiving epirubicin.

Contraindications: Patients should not receive epirubicin if ANC is less than 1,500/ mm³, cardiac dysfunction exists (e.g., insuf-

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