Doxotor® for IV Injection

Doxorubicin Hydrochloride for Injection USP

DESCRIPTION

Doxotor® for IV Injection is a preparation of Doxorubicin Hydrochloride. Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius var. caesius*. The cytotoxic effect of Doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of Doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of Doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of Doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of Doxorubicin by a variety of oxidases, reductases and dehydrogenases generates highly reactive species including the hydroxyl free radical $OH^{\bullet}$. Free radical formation has been implicated in Doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with Doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

INDICATIONS

- Acute lymphoblastic leukemia
- Acute myeloblastic leukemia
- Wilms' tumor
- Neuroblastoma
- Soft tissue and bone sarcoma
- Breast carcinoma
- Ovarian carcinoma
- Transitional cell bladder carcinoma
- Thyroid carcinoma
- Gastric carcinoma
- Hodgkin's disease
- Malignant lymphoma
- Bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types.

DOSAGE AND ADMINISTRATION

The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration.

Doxorubicin has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease, combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated. When used in combination with other chemotherapy drugs, the most commonly used dosage of Doxorubicin is 40 to 60 mg/m^2 given as a single intravenous injection every 21 to 28 days.

Dose Modifications

Patients in the NSABP B-15 study could have dose modifications of AC to 75% of the starting doses for neutropenic fever/infection. When necessary, the next cycle of treatment cycle was delayed until the absolute neutrophil count (ANC) was ≥1000 cells/mm^3 and the platelet count was ≥100, 000 cells/mm^3 and nonhematologic toxicities had resolved.

Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

Serum Bilirubin Levels	Recommended Dose
1.2 – 3.0 mg/100mL	50% Normal dose
> 3.0 mg/100mL	25% Normal dose

Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of Doxorubicin. Until specific compatibility data are available, it is not recommended that Doxorubicin be mixed with other drugs.

CONTRAINDICATIONS

- History of hypersensitivity
- Baseline Neutrophil count <1500 cells/mm^3
- Severe hepatic impairment
- Recent myocardial infarction
- Severe myocardial insufficiency
- Severe arrhythmias
- Previous treatment with complete cumulative doses of Doxorubicin, Daunorubicin, Idarubicin, and/or other anthracyclines and anthracenediones

SIDE EFFECTS

- Cutaneous: alopecia, Hyperpigmentation of nailbeds and dermal creases, onycholysis
- Gastrointestinal – Acute nausea and vomiting, Mucositis, Anorexia, abdominal pain, dehydration, diarrhea, hyperpigmentation of the oral mucosa
- Hypersensitivity – Fever, chills, and urticaria
- Neurological – Peripheral neurotoxicity

WARNING AND PRECAUTION

Severe local tissue necrosis will occur if there is extravasation during administration. Doxorubicin must not be given by the intramuscular or subcutaneous route. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure (CHF) may occur either during therapy or months to years after termination of therapy. Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) have been reported in patients treated with anthracyclines, including Doxorubicin.

Doxorubicin is not an anti-microbial agent. Doxorubicin is emetigenic. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of Doxorubicin, particularly when given in conjunction with other emetigenic drugs. Doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving Doxorubicin after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as Trastuzumab, may also be at an increased risk of developing cardiotoxicity. Physicians should avoid Doxorubicin-based therapy for up to 24 weeks after stopping Trastuzumab when possible.

USE IN PREGNANCY AND LACTATION

Pregnancy Category D. There are no adequate and well-controlled studies in pregnant women. If Doxorubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

Doxorubicin and its major metabolite, Doxorubicinol, have been detected in the milk of at least one lactating patient. Because of the potential for serious adverse reactions in nursing infants from Doxorubicin, mothers should be advised to discontinue nursing during Doxorubicin therapy.

PHARMACEUTICAL PRECAUTION

Do not store above 25 °C temperature. Keep away from light and wet place. Keep out of reach of children.

INSTRUCTIONS FOR RECONSTITUTION (AND FURTHER DILUTION)

The approved diluent for reconstitution of Doxorubicin Hydrochloride sterile powder is Sodium Chloride 9 mg/mL (0.9%) solution for injection and water for injection.

1. Use aseptic technique during the reconstitution and any further dilution of Doxorubicin Hydrochloride for intravenous infusion administration.

2. To reconstitute, slowly add the appropriate volume of sterile Sodium Chloride 9 mg/mL (0.9%) solution for injection or water for injection (as stated in the table below) and shake to dissolve.

Presentation	Volume of sterile Sodium Chloride (0.9%) solution for injection or water for injection to be added	Final concentration
10 mg	5 mL	2 mg/mL
50 mg	25 mL	2 mg/mL

3. Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if the solution is discolored, cloudy, or contains particulate matter.

4. It is recommended that Doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection. The tubing should be attached to a butterfly needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein, and the dosage. However, the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and, if this occurs, the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Reconstituted Solution Stability

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and under normal room light (100 foot-candles) and 15 days under refrigeration (2° to 8°C).

Chemical and physical in-use stability of solutions in the range 0.05 mg/mL to 2 mg/mL in 0.9% sodium chloride solution has been demonstrated for 7 days at room temperature (15-25 °C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at (2° to 8°C), unless reconstitution has taken place in controlled and validated aseptic conditions.

PACKAGING

Doxotor® 10 for IV Injection : Each box contains 1 vial of Doxorubicin Hydrochloride USP 10 mg (as lyophilized powder).

Doxotor® 50 for IV Injection : Each box contains 1 vial of Doxorubicin Hydrochloride USP 50 mg (as lyophilized powder).

SK+F ONCOLOGY

Manufactured by
ESKAYEF PHARMACEUTICALS LIMITED
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