

For the use of only Oncologist or a Cancer Hospital or a laboratory
Doxorubicin Hydrochloride Liposome Injection 2 mg/ml
KEMODOXA

COMPOSITION

Each ml contains:

Doxorubicin Hydrochloride IP.....2 mg

Water for Injection IP.....q.s.

Added Substances: Distearoylphosphatidylcholine (DSPC), Cholesterol BP, Sucrose IP, Histidine BP, Ammonium Sulfate USP NF, Sodium Hydroxide IP or Hydrochloric Acid IP

DESCRIPTION

KEMODOXA is a sterile translucent red liquid containing Doxorubicin Hydrochloride encapsulated in liposomes. Doxorubicin Hydrochloride is a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*. Liposomes are microscopic vesicles composed of phospholipid bilayer that is capable of encapsulating active drugs.

Each **KEMODOXA** vial, 10 ml and 25 ml fill respectively contains 20 mg and 50 mg Doxorubicin Hydrochloride and presented as a concentrate for infusion for single intravenous use.

Liposomal encapsulation can substantially affect a drug's functional properties relative to those of the unencapsulated drug. In addition, different liposomal drug products may vary from one another in a chemical composition and physical form of the liposomes. Such different can substantially affect the functional properties of liposomal drug products. **Do not substitute KEMODOXA with other products containing Doxorubicin Hydrochloride.**

MECHANISM OF ACTION

The mechanism of action of Doxorubicin Hydrochloride is related to the ability of the antibiotic to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration by the antibiotic and its main localization is in the perinucleolar chromatin. Rapid inhibition of mitotic activity and nucleic acid synthesis have also been demonstrated together with the appearance of chromosomal aberrations.

PRECLINICAL STUDIES

Animal studies on **KEMODOXA** have shown that the cytotoxic agent is active in a spectrum of experimental tumours. Preclinical studies have proved that it does not give rise to any of the toxic effects such as cardiac toxicity and myelosuppression. These toxic effects have been commonly observed with the administration of free drug.

In studies performed after repeated administration of KEMODOXA to dogs, no dermal inflammations and ulcer formations were observed which are the dose limiting factors for Pegylated liposomes.

CLINICAL PHARMACOLOGY

KEMODOXA is a liposomal formulation of Doxorubicin hydrochloride that provides greater concentration of Doxorubicin at tumour site because of longer circulation in blood. DSPC used in the formulation is a phospholipid of high phase transition temperature which increases retention of the liposomal content. This allows the doxorubicin hydrochloride liposomes to circulate for prolonged periods in the blood stream. Liposomes are small enough (average diameter of approximately 100 nm) to pass intact (extravasate) through defective blood vessels present in the tumours. Evidence of effectiveness has been seen in mice with Human A121 Ovarian carcinoma and Human Colon DLD1 Carcinoma tumours. **KEMODOXA** liposomes also have combination of low permeability lipid matrix and internal aqueous buffer system to keep encapsulated Doxorubicin hydrochloride intact during residence time in circulation.

PHARMACOKINETICS

The plasma pharmacokinetics of **KEMODOXA** in human has been found to be significantly different from the one that is reported in literature for conventional Doxorubicin Hydrochloride Injections.

INDICATIONS

KEMODOXA is indicated;

- As monotherapy for patients with Metastatic Breast Cancer where there is an increased Cardiac Risk.
- For the treatment of Metastatic Breast Cancer in women for whom an anthracycline would be considered.
- For the treatment of Metastatic Breast Cancer in women who have failed a Taxane containing regimen.
- For the treatment of metastatic carcinoma of the ovary in patients with diseases refractory to both Paclitaxel and Platinum based chemotherapy.
- For the treatment of AIDS- related Kaposi's sarcoma.

CONTRAINDICATIONS

KEMODOXA (DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION) is contraindicated in patients who have history of hypersensitivity reactions to conventional formulations of Doxorubicin Hydrochloride or any of the components of **KEMODOXA**.

WARNINGS

Warnings related to the use of conventional Doxorubicin Hydrochloride formulations should be observed. Special attention must be given to the cardiac toxicity exhibited by Doxorubicin Hydrochloride. Acute left ventricular failure can occur with Doxorubicin, particularly in patients who have received total Doxorubicin dosage exceeding the currently recommended limit of 550 mg/m². Lower (400 mg/m²) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardio toxic agents such as cyclophosphamide. Caution should be observed in patients who have received other anthracyclines and the total dose of Doxorubicin Hydrochloride given should take into account any previous or concomitant therapy with other anthracyclines or related compounds. Congestive heart failure and/or cardiomyopathy may be encountered after discontinuation of therapy. In patients with a history of cardiovascular disease, **KEMODOXA** should be administered only when the potential benefits of treatment outweigh the risk. Cardiac function should be carefully monitored in patients treated with **KEMODOXA**. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or gated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity during **KEMODOXA** therapy. If these test results indicate possible cardiac injury associated with **KEMODOXA** therapy, the benefits of continued therapy must be carefully weighed against the risk of myocardial injury.

PRECAUTIONS:

Patients receiving therapy with **KEMODOXA** should be monitored by a Physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are manageable with dose reductions or delays. (See Dosage and Administration) Laboratory Tests such as Complete blood counts including platelet counts should be carried out frequently. Prior to administration of each dose of **KEMODOXA** blood counts are required to be monitored.

If the patient experiences early symptoms or signs of infusion reaction, immediately discontinue the infusion, give appropriate premeditation (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

Do not administer **KEMODOXA** as a bolus injection or as undiluted solution. It is recommended that the **KEMODOXA** infusion line be connected through the side port of an intravenous infusion of Dextrose 5% in water to achieve further dilution and minimize the risk of thrombosis and extravasation. **KEMODOXA** must not be given by the intramuscular or subcutaneous route. Do not use with in-line filters during administration.

DRUG INTERACTIONS

It is not recommended that **KEMODOXA** be mixed with other drugs. **KEMODOXA** may interact with the conventional formulation of Doxorubicin Hydrochloride.

Nursing Mothers - It is not known whether this drug is excreted in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from **KEMODOXA**, mothers should discontinue nursing prior to taking this drug.

DOSAGE AND ADMINISTRATIONS

Breast Cancer / Ovarian Cancer Patients: **KEMODOXA** should be administered intravenously at a dose of $50\text{mg}/\text{m}^2$ (Doxorubicin Hydrochloride equivalent) at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse effects are observed, the rate of infusion can be increased to complete administration of the drug over one hour. The patient should be administered one dose every 4 weeks. The therapy should be continued till no evidence of cardiotoxicity is seen and patient continues to tolerate the treatment. A minimum of 4 courses is recommended. To manage adverse events such as hematologic toxicity, the doses may be delayed or reduced. Pre-treatment with or concomitant use of antiemetic should be considered.

For doses <90 mg: dilute the product in 250 ml Dextrose 5% injection.

For doses >90 mg: dilute the product in 500 ml Dextrose 5% injection.

AIDS-KS Patients: **KEMODOXA** should be administered intravenously at a dose of $20\text{ mg}/\text{m}^2$ (Doxorubicin Hydrochloride equivalent) over 30 minutes diluted in 250 ml 5% Dextrose injection once every two to three weeks, intervals shorter than 10 days should be avoided as drug accumulation and increased toxicity cannot be ruled out for as long as patients respond satisfactorily and tolerate treatment. Do not administer as a bolus injection or as an undiluted solution. Rapid infusion may increase the risk of infusion-related reactions.

KEMODOXA should be considered as an irritant and precautions should be taken to avoid extravasation. With intravenous administration of **KEMODOXA**, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. **KEMODOXA** must not be given by the intramuscular or subcutaneous route.

Patients should be carefully monitored for toxicity. Adverse events, such as PPE, hematologic toxicities, and stomatitis may be managed by dose delays and adjustments.

Patients with Impaired Hepatic Function - Limited clinical experience exists in treating hepatically impaired patients with **KEMODOXA**. Based on experience with Doxorubicin Hydrochloride, it is recommended that **KEMODOXA** dosage be reduced if the bilirubin is elevated as follows: Serum bilirubin 1.2 to 3.0 mg/dL administers 1/2 of normal dose, >3 mg/dL administer 1/4 of normal dose.

ADMINISTRATION

The appropriate dose of **KEMODOXA**, up to a maximum of 90 mg, must be diluted in 250 ml of 5% Dextrose Injection, prior to administration. If the dose exceeds 90 mg, dilute with 500ml of 5% Dextrose injection. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in **KEMODOXA**. Diluted **KEMODOXA** should be refrigerated at 2°C to 8°C (36°F to 46°F) if not used immediately and administered within 24 hours. Do not use with inline filters. Do not mix with other drugs. Do not use any diluent other than 5% Dextrose Injection. Do not use any bacteriostatic agent, such as benzyl alcohol. **KEMODOXA** is not a clear solution but a translucent, red liposomal dispersion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if a precipitate or foreign matter is present.

STORAGE AND STABILITY

Refrigerate unopened **KEMODOXA** vials at 2 °C to 8°C (36°F to 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products.

PROCEDURE FOR PROPER HANDLING AND DISPOSAL

KEMODOXA should not be handled by pregnant staff. Procedure for proper handling and disposal should be observed. Consideration should be given to handling and disposal according to guidelines used for cytotoxic drugs. Any spillage or waste material may be disposed of by incineration. Caution should be exercised in while the handling and preparing the solution of **KEMODOXA**. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If **KEMODOXA** comes in contact with skin wash thoroughly with soap and water. In the event of contact with the eyes, rinse them thoroughly with copious amounts of water. **KEMODOXA** should be considered as an irritant and precautions should be taken to avoid extravasation. With intravenous administration of **KEMODOXA**, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation occur, the infusion should be immediately terminated and restarted in another vein. **KEMODOXA** must not be given by the intramuscular or subcutaneous route. **KEMODOXA** should be handled and disposed off in a manner consistent with other anticancer drugs.

HOW SUPPLIED

KEMODOXA (Doxorubicin Hydrochloride Liposome Injection) is supplied as a sterile, translucent, red dispersion in 10 and 25 ml single use glass vials. Each vial of 10 ml and 25 ml contains respectively 20 mg and 50 mg Doxorubicin Hydrochloride available as individually packed vials.