SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

ADROSAL 10 mg (Doxorubicin hydrochloride 10 mg lyophilized powder for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains10mg Doxorubicin Hydrochloride

Excipient(s) with known effect:

Each tablet contains 50.0 mg anhydrous lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Lyophilized powder for Injection

A dark red lyophilized cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxorubicin has been used successfully both as a single agent and also in combination with other approved cancer chemotherapeutic agents to produce regression in neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumour, neuroblastomas, soft tissue sarcomas, bone sarcomas, breast carcinomas, gynecologic carcinomas, testicular carcinomas, bronchogenic carcinoma, Hodgkin's disease, non-Hodgkin's lymphoma, thyroid carcinoma, bladder carcinomas, squamous cell carcinoma of the head and neck and gastric carcinoma.

Doxorubicin has also been used by instillation into the bladder for the topical treatment of superficial bladder tumours. A number of other solid tumours have also shown some responsiveness to Doxorubicin alone or in combination with other drugs. Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinomas, brain tumors and metastases to the central nervous system not to be significantly responsive to Doxorubicin therapy.

4.2 Posology and method of administration

Dosage A variety of dose schedules has been used. The following recommendations are for use as a single agent only.

Intravenous (I.V.) Administration

The total doxorubicin dose per cycle may differ according to its use within a specific treatment regimen (e.g. given as a single agent or in combination with other cytotoxic drugs) and according

to the indication.

The most commonly used dosage schedule is 60-75 mg/m^2 as a single intravenous injection administered at 21-day intervals. An alternative dose schedule is weekly doses of 20 mg/m^2 which has been reported to produce a lower incidence of congestive heart failure. A dose of 30 mg/m^2 on each of three successive days repeated every 4 weeks has also been used.

Hepatic Dysfunction. Doxorubicin dosage must be reduced if the bilirubin is elevated as follows: Serum Bilirubin 1.2-3.0 mg/dL -- give ½ of recommended starting dose, > 3 mg/dL -- give ¼ of recommended starting dose. Doxorubicin should not be administered to patients with severe hepatic impairment.

Other Special Populations. Lower starting doses or longer intervals between cycles may need to be considered for heavily pretreated patients, children, elderly patients, obese patients, or patients with neoplastic bone marrow infiltration.

Intravesical Administration

When Doxorubicin is instilled intravesically for the treatment of superficial bladder carcinomas, the usual dose employed ranges from 50-80 mg in a total volume of 50-100 mL of 0.9% Sodium Chloride Solution USP with a contact time of 1-2 hours. Care should be taken to ensure that the tip of the catheter is in the bladder cavity before instilling the Doxorubicin solution. Instillation is repeated weekly for 4 weeks and subsequently at monthly intervals. Therapy may continue for one year or longer as no significant systemic toxicity has been reported. Care should be exercised in the handling and disposal of the voided urine. PVC gloves should be worn and the urine should be inactivated by decolourizing it with 10 mL or more of sodium hypochlorite solution (household bleach).

Other methods of administration have been investigated including intra-arterial administration and also continuous or long term intravenous infusion utilizing appropriate infusion pumps.

ADMINISTRATION:

Intravenous Administration

Care in the administration of Doxorubicin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and 12 erythematous streaking. On intravenous administration of Doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation even if the blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein.

If it is known or suspected that subcutaneous extravasation has occurred, the following steps are recommended:

- Attempt aspiration of the infiltrated Doxorubicin solution.
- Local intermittent application of ice for up to 3 days.
- Elevation of the affected limb.
- Close observation of the lesion.
- Consultation with a plastic surgeon familiar with drug extravasations if local pain persists or skin changes progress after 3 to 4 days. If ulceration begins, early wide excision of the involved area should be considered.

Doxorubicin 10 mg vial should be reconstituted with 5 mL of 0.9% Sodium Chloride Solution USP to give a final concentration of 2 mg/mL of doxorubicin hydrochloride. Bacteriostatic diluents are not recommended.

After adding the diluent, the vial should be shaken until the contents are dissolved. A slight suspension may form which will completely dissolve on further shaking. The vials are under negative pressure and care should be taken to avoid a pressure build up. To minimize aerosol formation during reconstitution; particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution should also be avoided. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration 2-8^{o}C. The solution should be protected from exposure to direct light. For single dose vials, any unused solution should be discarded.

Doxorubicin should be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Solution USP (0.9%) or 5% Dextrose Solution USP. The tubing should be attached to a Butterfly* needle, or other suitable device and 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 dosage should be administered for not less than 3 minutes and not more than 10 minutes to minimize the risk of thrombosis or perivenous extravasation. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A direct push injection is not 13 recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.
Unless specific compatibility data are available, the mixing of Doxorubicin solutions with other drugs is not recommended. Precipitation occurs with 5-fluorouracil and heparin.

Intravesical administration

Doxorubicin should be instilled using a catheter and retained intravesically for 1 to 2 hours. Care should be taken to ensure that the tip of the catheter is in the bladder cavity before instilling the Doxorubicin solution. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation.

4.3 Contraindications

- Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones such as epirubicin hydrochloride, daunorubicin hydrochloride, mitoxantrone or mitomycin C.
- marked persistent myelosupression induced by prior treatment with other antitumor agents or by radiotherapy
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- history of severe cardiac disease
- previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin and/or other anthracyclines and anthracenediones

Intravesical use:

- invasive tumors that have penetrated the bladder wall
- urinary infections
- inflammation of the bladder

4.4 Special warnings and precautions for use

Doxorubicin hydrochloride is a potent drug and should be used only by physicians experienced with cancer chemotherapy drugs. Blood counts and hepatic function tests should be performed regularly. Because of the experience with cardiac toxicity, it is not recommended to exceed a total dose of adriamycin 550 mg/m^2 with the 21 day regimen and 700 mg/m^2 with the weekly regimen. cardiac monitoring is advised in those patients who have received mediastinal radiotherapy, other anthracycline or anthracene therapy, with pre-existing cardiac disease, or

who have received prior adriamycin cumulative doses exceeding 400 mg/m^2 with the 21 day regimen and 550 mg/m^2 utilizing the weekly regimen.

PRECAUTIONS

Initial treatment with Doxorubicin requires close observation of the patient and extensive laboratory monitoring. Like other cytotoxic drugs, Doxorubicin may induce hyperuricemia secondary to rapid lysis of neoplastic cells, particularly in patients with leukemia. The clinician should monitor the patient's serum chemistry and blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem. Hydration, urine alkalinization and allopurinol administration will help to prevent or minimize potential complications of tumor-lysis syndrome. The systemic clearance of Doxorubicin has been found to be reduced in obese patients (i.e., > 130% ideal body weight), Other Special Populations). Doxorubicin is not an anti-microbial agent.

4.5 Interaction with other medicinal products and other forms of Interaction

Doxorubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastrointestinal effects. The use of Doxorubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment. Changes in hepatic function induced by concomitant therapies may affect Doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

4.6 Pregnancy and lactation

The embryotoxic potential of Doxorubicin was confirmed in vitro and in vivo. When given to female rats before and during mating, pregnancy, and lactation, Doxorubicin was toxic to both dams and fetuses. Doxorubicin has been implicated in causing fetal harm when administered to a pregnant woman. If a woman receives Doxorubicin during pregnancy or becomes pregnant while taking the drug, she should be informed of the potential hazard to the fetus. Doxorubicin is secreted into breast milk. Mothers should not breast-feed while undergoing chemotherapy with Doxorubicin.

4.7 Effects on ability to drive and use machines

Doxorubicin could affect your ability to drive and operate machinery.

4.8 Undesirable effects

The following adverse events have been reported in association with Doxorubicin therapy:

Cardiovascular: sinus tachycardia, ECG abnormalities, tachyarrhythmias, atrioventricular and bundle branch block, asymptomatic reductions in left ventricular ejection fraction, congestive heart failure

Hematologic: leukopenia, neutropenia, anemia, thrombocytopenia, hemorrhage

Gastrointestinal: anorexia, nausea/vomiting, dehydration, mucositis/stomatitis, hyperpigmentation of the oral mucosa, esophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, diarrhea, colitis

Liver: changes in transaminase levels, hyperuricemia

Endocrine: amenorrhea, hot flashes, oligospermia, azoospermia

Ocular: conjunctivitis/keratitis, lacrimation

Skin: alopecia, local toxicity, rash/itch, skin changes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin ('radiation recall reaction'), urticaria, acral erythema

Vascular: phlebitis, thrombophlebitis, thromboembolism

Urological: red coloration of urine for 1 to 2 days after administration

Bladder, local: pain, hemorrhage, and occasionally decreased bladder capacity upon instillation

Local: severe cellulitis, vesication, tissue necrosis upon extravasation, erythematous streaking along the vein proximal to the site of the injection

Other: anaphylaxis, infection, sepsis/septicemia, acute lymphocytic leukemia, acute myelogenous leukemia, malaise/asthenia, fever, chills, shock, cross sensitivity to lincomycin.

4.9 Overdose

Acute overdosage with Doxorubicin enhances the toxic effects of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis. Acute overdosage with Doxorubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac alterations. Chronic overdosage with cumulative doses exceeding 550 mg/m^2 increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The mechanism of action of Doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a wide spectrum of experimental tumours, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy of testes in rats and dogs.

5.2 Pharmacokinetic properties

Pharmacokinetic studies show that the intravenous administration of normal or radio labelled Doxorubicin hydrochloride for injection is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4-5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40-50% of the administered dose being recovered in the bile or the feces in seven days. Impairment of liver function results in slower excretion, and, consequently, increased retention and accumulation in plasma and tissues. Doxorubicin does not cross the blood brain barrier.

5.3 Preclinical safety data

None Stated.

5.4 Carcinogenesis & Mutagenesis, Impairment of Fertility

Doxorubicin was genotoxic in a battery of in vitro or in vivo tests. An increase in the incidence of mammary tumors was reported in rats, and a trend for delay or arrest of follicular maturation was seen in female dogs. In women, Doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur. Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia. Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing Doxorubicin treatment should use effective contraceptive methods.

Pregnancy and Lactation

The embryotoxic potential of Doxorubicin was confirmed in vitro and in vivo. When given to female rats before and during mating, pregnancy, and lactation, Doxorubicin was toxic to both dams and fetuses. Doxorubicin has been implicated in causing fetal harm when administered to a pregnant woman. If a woman receives Doxorubicin during pregnancy or becomes pregnant while taking the drug, she should be informed of the potential hazard to the fetus. Doxorubicin is secreted into breast milk. Mothers should not breast-feed while undergoing chemotherapy with Doxorubicin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl Paraben
Anhydrous Lactose
Sodium Hydroxide
Sterile Water for Injection

6.2 Incompatibilities

Unless specific compatibility data are available, Doxorubicin should not be mixed with other drugs. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of Doxorubicin. Doxorubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation. Precipitation also occurs with 5-fluorouracil.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25^0C. Protected from light.

6.5 Nature and contents of container

5 ml Flint tubular glass vial, which is closed with a 20 mm slotted rubber plug and finally sealed with 20 mm aluminum flip off seal is packed in a carton along with leaflet.

6.6 Special precautions for disposal and other handling:

Dispose off the material as per local federal regulations for handling and disposal of cytotoxic products.

7. MARKETING AUTHORIZATION HOLDER

M/S VHB MEDI SCIENCES LTD.

50 AB, Govt industrial Estate,

Charkop, Kandivali (W)

Mumbai-400067, INDIA

Manufacturing site:

VHB MEDI SCIENCES LTD.

Plot No.20-22 & 49-51, IIE, Sector-5,

SIDCUL, Pantnagar, Udham Singh Nagar,

Uttarakhand, INDIA.

8. MARKETING AUTHORIZATION NUMBER

08586/07815/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

13/04/2023

10. DATE OF REVISION OF THE TEXT

18/07/2023