SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxorubicin Hydrochloride Injection USP (ADRIM)

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Doxorubicin Hydrochloride USP 2 mg

3. PHARMACEUTICAL

FORM Sterile Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adjuvant Breast Cancer

Doxorubicin Hydrochloride Injection is indicated as a component of multi-agent adjuvant chemotherapy for treatment of women with axillary lymph node involvement following resection of primary breast cancer

Other Cancers

Doxorubicin Hydrochloride Injection is indicated for the treatment of:

- acute lymphoblastic leukemia
- acute myeloblastic leukemia
- Hodgkin lymphoma
- non-Hodgkin lymphoma (NHL)
- metastatic breast cancer
- metastatic Wilms' tumor
- metastatic neuroblastoma
- metastatic soft tissue sarcoma
- metastatic bone sarcoma
- metastatic ovarian carcinoma
- metastatic transitional cell bladder carcinoma
- metastatic thyroid carcinoma
- metastatic gastric carcinoma
- metastatic bronchogenic carcinoma

4.2 Posology and method of administration Recommended Dose

Recommended Dosage for Adjuvant Breast Cancer

The recommended dose of doxorubicin hydrochloride is 60 mg/m2 administered as an intravenous bolus on day 1 of each 21-day treatment cycle, in combination with cyclophosphamide, for a total of four cycles.

Recommended Dosage for Other Cancers

The recommended dosage of doxorubicin hydrochloride injection when used as a single agent is 60 to 75 mg/m2 intravenously every 21 days.

The recommended dosage of doxorubicin hydrochloride injection, when administered in combination with other chemotherapy drugs, is 40 to 75 mg/m2 intravenously every 21 to 28 days.

Consider use of the lower doxorubicin hydrochloride injection dose in the recommended dose range or longer intervals between cycles for heavily pretreated patients, elderly patients, or obese patients.

Cumulative doses above 550 mg/m2 are associated with an increased risk of

Plasma bilirubin concentration (mg/dL)	Dosage reduction (%)
1.2 - 3.0	50
3.1 - 5.0	75
greater than 5.0 mg/dL	Do not initiate doxorubicin hydrochloride injection Discontinue doxorubicin hydrochloride injection

cardiomyopathy.

Dose Modifications

Cardiac Impairment

Discontinue doxorubicin in patients who develop signs or symptoms of cardiomyopathy.

Hepatic Impairment

Doxorubicin hydrochloride is contraindicated in patients with severe hepatic impairment (Child- Pugh Class C or serum bilirubin >5.0 mg/dL).

Decrease the dose of doxorubicin hydrochloride in patients with elevated serum total bilirubin concentrations as follows:

Preparation and Administration

Dilution of Doxorubicin Hydrochloride Injection

Dilute doxorubicin hydrochloride solution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

Protect from light following preparation until completion of infusion.

Administration

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.

Administration by Intravenous Injection

Administer doxorubicin hydrochloride as an intravenous injection through a central intravenous line or a secure and free-flowing peripheral venous line containing 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.

Administer doxorubicin hydrochloride intravenously over 3 to 10 minutes. Decrease the rate of doxorubicin hydrochloride administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur.

Administration by Continuous Intravenous Infusion:

Administer diluted Doxorubicin Hydrochloride Injection solution only through a central intravenous line. Decrease the rate of doxorubicin hydrochloride administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur.

Protect from light from preparation for infusion until completion of infusion.

Management of Suspected Extravasation

Discontinue doxorubicin hydrochloride for burning or stinging sensation or other evidence indicating perivenous infiltration or extravasation. Manage confirmed or suspected extravasation as follows:

Do not remove the needle until attempts are made to aspirate extravasated fluid.

Do not flush the line.

Avoid applying pressure to the site.

Apply ice to the site intermittently for 15 min 4 times a day for 3 days.

If the extravasation is in an extremity, elevate the extremity.

In adults, consider administration of dexrazoxane

4.3 Contraindications

Doxorubicin hydrochloride is contraindicated in patients with:

Severe myocardial insufficiency

Recent (occurring within the past 4-6 weeks) myocardial infarction

Severe persistent drug-induced myelosuppression

Severe hepatic impairment (defined as Child Pugh Class C or serum bilirubin level

greater than 5 mg/dL)

Severe hypersensitivity reaction to doxorubicin hydrochloride including anaphylaxis.

4.4 Special warnings and precautions for use Cardiomyopathy and Arrhythmias

Cardiomyopathy

Doxorubicin hydrochloride can result in myocardial damage, including acute left ventricular failure. The risk of cardiomyopathy is generally proportional to the cumulative exposure. Include prior doses of other anthracyclines or anthracenediones in calculations of total cumulative dosage for doxorubicin hydrochloride. Cardiomyopathy may develop during treatment or up to several years after completion of treatment and can include decrease in LVEF and signs and symptoms of congestive heart failure (CHF). The probability of developing cardiomyopathy is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m2 of doxorubicin hydrochloride, 3 to 5% at a dose of 400 mg/m2, 5 to 8% at a dose of 450 mg/m2, and 6 to 20% at a dose of 500 mg/m2, when doxorubicin hydrochloride is administered every 3 weeks. There is an additive or potentially synergistic increase in the risk of cardiomyopathy in patients who have received radiotherapy to the mediastinum or concomitant therapy with other known cardiotoxic agents such as cyclophosphamide and trastuzumab. Pericarditis and myocarditis have also been reported during or following doxorubicin hydrochloride treatment. Assess left ventricular cardiac function (e.g., MUGA or echocardiogram) prior to initiation of doxorubicin hydrochloride, during treatment to detect acute changes, and after treatment to detect delayed cardiotoxicity. Increase the frequency of assessments as the cumulative dose exceeds 300 mg/m2. Use the same method of assessment of LVEF at all time points. Consider the use of dexrazoxane to reduce the incidence and severity of cardiomyopathy due to doxorubicin hydrochloride administration in patients who have received a cumulative doxorubicin

hydrochloride dose of 300 mg/m2 and who will continue to receive doxorubicin hydrochloride.

Arrhythmias

Doxorubicin hydrochloride can result in arrhythmias, including life-threatening arrhythmias, during or within a few hours after doxorubicin hydrochloride administration and at any time point during treatment. Tachyarrhythmias, including sinus tachycardia, premature ventricular contractions, and entricular tachycardia, as well as bradycardia may occur. Electrocardiographic changes including non-specific ST-T wave changes, atrioventricular and bundle-branch block can also occur. These electrocardiographic changes may be transient and self-limited and may not require dose-modifications of doxorubicin hydrochloride.

Secondary Malignancies

The risk of developing secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) is increased following treatment with doxorubicin hydrochloride. Cumulative incidences ranged from 0.2% at five years to 1.5% at 10 years in two separate trials involving the adjuvant treatment of women with breast cancer. These leukemias generally occur within 1 to 3 years of treatment.

Extravasation and Tissue Necrosis

Extravasation of doxorubicin hydrochloride can result in severe local tissue injury manifesting as blistering, ulceration, and necrosis requiring wide excision of the affected area and skin grafting. When given via a peripheral venous line, infuse doxorubicin over 10 minutes or less to minimize the risk of thrombosis or perivenous extravasation. If signs or symptoms of extravasation occur, immediately terminate the injection or infusion. Extravasation may be present in patients who do not experience a stinging or burning sensation or when blood return is present on aspiration of the infusion needle. If extravasation is suspected, apply ice to the site intermittently for 15 minutes, 4 times a day for 3 days. If appropriate, administer dexrazoxane at the site of extravasation as soon as possible and within the first 6 hours after extravasation.

Severe Myelosuppression

Doxorubicin hydrochloride can cause myelosuppression. In Study 1, the incidence of severe myelosuppression was: grade 4 leukopenia (0.3%), grade 3 leukopenia (3%), and grade 4 thrombocytopenia (0.1%). A dose-dependent, reversible neutropenia is the predominant manifestation of hematologic toxicity from doxorubicin hydrochloride. When doxorubicin hydrochloride is administered every 21 days, the neutrophil count reaches its nadir 10 to 14 days after administration with recovery usually occurring by the 21st day.

Obtain baseline assessment of blood counts and carefully monitor patients during treatment for possible clinical complications due to myelosuppression.

Use in Patients with Hepatic Impairment

The clearance of doxorubicin is decreased in patients with elevated serum bilirubin with an increased risk of toxicity. Reduce the dose of doxorubicin hydrochloride in patients with serum bilirubin levels of 1.2-5.0 mg/dL.

Doxorubicin is contraindicated in patients with severe hepatic impairment (defined as Child Pugh Class C or serum bilirubin level greater than 5 mg/dL).

Obtain liver tests including SGOT, SGPT, alkaline phosphatase, and bilirubin prior to and during doxorubicin hydrochloride therapy

Tumor Lysis Syndrome

Doxorubicin hydrochloride may induce tumor lysis syndrome in patients with rapidly growing tumors. Evaluate blood uric acid levels, potassium, calcium, phosphate, and creatinine after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor lysis syndrome.

Potentiation of Radiation Toxicity and Radiation Recall

Doxorubicin hydrochloride can increase radiation-induced toxicity to the myocardium, mucosa, skin, and liver. Radiation recall, including but not limited to cutaneous and pulmonary toxicity, can occur in patients who receive doxorubicin hydrochloride after prior radiation therapy.

Embryofetal Toxicity

Based on findings in animals and its mechanism of action, Doxorubicin Hydrochloride Injection can cause fetal harm when administered to a pregnant woman; avoid the use of Doxorubicin Hydrochloride Injection during the 1st trimester. Available human data do not establish the presence or absence of major birth defects and miscarriage related to the use of doxorubicin hydrochloride during the 2nd and 3rd trimesters. Doxorubicin hydrochloride was teratogenic and embryotoxic in rats and rabbits at doses lower than the recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Doxorubicin Hydrochloride Injection and for 6 months after treatment. Advise males with female partners of reproductive potential to use effective contraception during treatment with Doxorubicin Hydrochloride Injection and for 3 months after treatment. Advise males with pregnant partners to use condoms during treatment with Doxorubicin Hydrochloride Injection and for at least 10 days after the final dose.

Pediatric Use

Based on observations, pediatric patients treated with doxorubicin hydrochloride are at risk for developing late cardiovascular dysfunction. Risk factors include young age at treatment (especially < 5 years), high cumulative doses and receipt of combined modality therapy. Long- term periodic cardiovascular monitoring is recommended for all pediatric patients who have received doxorubicin hydrochloride. Doxorubicin hydrochloride, as a component of intensive chemotherapy regimens administered to pediatric patients, may contribute to prepubertal growth failure and may also contribute to gonadal impairment, which is usually temporary.

There are no recommended dose adjustments based on age. Doxorubicin clearance was increased in patients aged 2 years to 20 years as compared to adults, while doxorubicin clearance was similar in children less than 2 years as compared to adults.

Geriatric Use

Clinical experience in patients who were 65 years of age and older who received doxorubicin hydrochloride-based chemotherapy regimens for metastatic

breast cancer showed no overall differences in safety and effectiveness compared with younger patients.

4.5 Interaction with other medicinal products and other forms of interaction Effect of Other Drugs on Doxorubicin Hydrochloride Injection

Inhibitors of CYP3A4, CYP2D6, and P-gp

Concomitant use of doxorubicin hydrochloride with inhibitors of CYP3A4, CYP2D6, or P- glycoprotein (P-gp), increased concentrations of doxorubicin, which may increase the incidence and severity of adverse reactions of doxorubicin hydrochloride. Avoid concomitant use of Doxorubicin Hydrochloride Injection with inhibitors of CYP3A4, CYP2D6, or P-gp.

Inducers of CYP3A4, CYP2D6, or P-gp

Concomitant use of doxorubicin hydrochloride with inducers of CYP3A4, CYP2D6, or P-gp may decrease the concentration of doxorubicin. Avoid concomitant use of Doxorubicin Hydrochloride Injection with inducers of CYP3A4, CYP2D6, or P-gp.

Paclitaxel

Paclitaxel, when given prior to doxorubicin hydrochloride, increases the plasma-concentrations of doxorubicin and its metabolites. Administer Doxorubicin Hydrochloride Injection/for Injection prior to paclitaxel if used concomitantly.

Concomitant Use of Trastuzumab

Concomitant use of trastuzumab and doxorubicin hydrochloride results in an increased risk of cardiac dysfunction. Avoid concurrent administration of doxorubicin and trastuzumab. The appropriate interval for administering doxorubicin following trastuzumab therapy has not been determined

Patients receiving doxorubicin after stopping treatment with trastuzumab may also be at an increased risk of developing cardiotoxicity. Trastuzumab may persist in the circulation for up to 7 months. Therefore, avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, carefully monitor cardiac function.

Concomitant Use of Dexrazoxane

Do not administer dexrazoxane as a cardioprotectant at the initiation of doxorubicin hydrochloride containing chemotherapy regimens. In a randomized trial in women with metastatic breast cancer, initiation of dexrazoxane with doxorubicin hydrochloride-based chemotherapy resulted in a significantly lower tumor response rate (48% vs. 63%; p=0.007) and shorter time to progression than in women who received doxorubicin hydrochloride-based chemotherapy alone.

Concomitant Use of 6-Mercaptopurine

Doxorubicin hydrochloride may potentiate 6-mercaptopurine-induced hepatotoxicity. In 11 patients with refractory leukemia treated with 6-mercaptopurine (500 mg/m2 intravenously daily for 5 days per cycle every 2-3 weeks) and doxorubicin hydrochloride (50 mg/m2 intravenous

once per cycle every 2-3 weeks) alone or with vincristine and prednisone, all developed hepatic dysfunction manifested by elevations of total serum bilirubin, alkaline phosphatase and aspartate aminotransferase.

4.6 Fertility, pregnancy and lactation Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, Doxorubicin Hydrochloride Injection can cause fetal harm when administered to a pregnant woman; avoid the use of Doxorubicin Hydrochloride Injection during the 1st trimester. Available human data do not establish the presence or absence of major birth defects and miscarriage related to the use of doxorubicin hydrochloride during the 2nd and 3rd trimesters. Doxorubicin hydrochloride was teratogenic and embryotoxic in rats and embryotoxic in rabbits when administered during organogenesis at doses approximately 0.07 times (based on body surface area) the recommended human dose of 60 mg/m2 (see Data). Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

Doxorubicin hydrochloride was teratogenic and embryotoxic at doses of 0.8 mg/kg/day (about 0.07 times the recommended human dose based on body surface area) when administered during the period of organogenesis in rats. Teratogenicity and embryotoxicity were also seen using discrete periods of treatment. The most susceptible was the 6- to 9-day gestation period at doses of 1.25 mg/kg/day and greater. Characteristic malformations included esophageal and intestinal atresia, tracheo-esophageal fistula, hypoplasia of the urinary bladder, and cardiovascular anomalies. Doxorubicin hydrochloride was embryotoxic (increase in embryofetal deaths) and abortifacient at 0.4 mg/kg/day (about 0.07 times the recommended human dose based on body surface area) in rabbits when administered during the period of organogenesis.

Lactation

Risk Summary

Doxorubicin was measured in the milk of one lactating patient after therapy with 70 mg/m2 of doxorubicin hydrochloride given as a 15-minute intravenous infusion. The peak milk concentration at 24 hours after treatment was 4.4-fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours. There are no data on the effects of doxorubicin hydrochloride on the breastfed child or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with Doxorubicin Hydrochloride Injection and for 10 days after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Doxorubicin Hydrochloride Injection.

Contraception

Females

Doxorubicin Hydrochloride Injection can cause fetal harm when administered to pregnant women. Advise female patients of reproductive potential to use highly effective contraception during treatment with Doxorubicin Hydrochloride Injection and for 6 months after treatment.

Males

Doxorubicin hydrochloride may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Due to the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with Doxorubicin Hydrochloride Injection and for 3 months after treatment. Males with pregnant partners should use condoms during treatment and for at least 10 days after the final dose.

Infertility

Females

In females of reproductive potential, doxorubicin hydrochloride may cause infertility and result in amenorrhea. Premature menopause can occur. Recovery of menses and ovulation is related to age at treatment.

Males

Doxorubicin hydrochloride may result in oligospermia, azoospermia, and permanent loss of fertility. Sperm counts have been reported to return to normal levels in some men. This may occur several years after the end of therapy.

4.7 Effect on ability to drive and use machines Not relevant

4.8 Undesirable effects

The following adverse reactions are discussed in more detail in other sections of the labelling..

Cardiomyopathy and Arrhythmias
Secondary Malignancies
Extravasation and Tissue Necrosis
Severe Myelosuppression
Tumor Lysis Syndrome
Radiation Sensitization and Radiation Recall

Clinical Trial Experience in Breast Cancer

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data below were collected from 1492 women who received doxorubicin hydrochloride at a of 60 mg/m2 and cyclophosphamide at a dose of 600 mg/m2 (AC) every 3

weeks for 4 cycles for the adjuvant treatment of axillary lymph node positive breast cancer. The median number of cycles received was 4. Selected adverse reactions reported in this study are provided in the below table. No treatment-related deaths were reported in patients on either arm of the study.

Table 1. Selected Adverse Reactions in Patients with Early Breast Cancer Involving Axillary Lymph Nodes

Adverse reactions, % of patients	AC*	Conventional CMF
	N=1492	N=739
Leukopenia Grade 3 (1,000–1,999 /mm3) Grade 4 (<1000 /mm3)	3.4 0.3	9.4 0.3
Thrombocytopenia Grade 3 (25,000–49,999 /mm3) Grade 4 (<25,000 /mm3)	0 0.1	0.3 0
Shock, sepsis	2	1
Systemic infection	2	1
Vomiting Vomiting 12 hours Vomiting >12 hours Intractable	34 37 5	25 12 2
Alopecia	92	71
Cardiac dysfunction Asymptomatic Transient Symptomatic	0.2 0.1 0.1	0.1 0 0

* Includes pooled data from patients who received either AC alone for 4 cycles, or who were treated with AC for 4 cycles followed by 3 cycles of CMF

Other Adverse Reactions

Cardiac – cardiogenic shock

Cutaneous –Skin and nail hyperpigmentation, oncolysis, rash, itching, photosensitivity, urticaria, acral erythema, palmar plantar erythrodysesthesia

Gastrointestinal – Nausea, mucositis, stomatitis, necrotizing colitis, typhlitis, gastric erosions, gastrointestinal tract bleeding, hematochezia, esophagitis, anorexia, abdominal pain, dehydration, diarrhea, hyperpigmentation of the oral mucosa

Hypersensitivity – Anaphylaxis

Laboratory Abnormalities –Increased alanine aminotransferase, increased aspartate aminotransferase

Neurological – Peripheral sensory and motor neuropathy, seizures, coma

Ocular – Conjunctivitis, keratitis, lacrimation

Vascular – Phlebosclerosis, phlebitis/thrombophlebitis, hot flashes, thromboembolism

Other – Malaise/asthenia, fever, chills, weight gain

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal

product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system. Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

Few cases of overdose have been described. A 58-year-old man with acute lymphoblastic leukemia received 10-fold overdose of doxorubicin hydrochloride (300 mg/m2) in one day. He
was treated with charcoal filtration, hemopoietic growth factor (G-CSF), proton pump inhibitor and antimicrobial prophylaxis. The patient suffered sinus tachycardia, grade 4 neutropenia and thrombocytopenia for 11 days, severe mucositis and sepsis. The patient recovered completely 26 days after the overdose. A 17-year-old girl with osteogenic sarcoma received 150 mg of doxorubicin hydrochloride daily for 2 days (intended dose was 50 mg per day for 3 days). The patient developed severe mucositis on days 4-7 after the overdose and chills and pyrexia on day 7. The patient was treated with antibiotics and platelets and recovered 18 days after overdose.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties Mechanism of action

The cytotoxic effect of doxorubicin hydrochloride 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 hydrochloride cytocidal activity.

Clinical efficacy and safety

The clinical efficacy of doxorubicin hydrochloride-containing regimens for the post-operative, adjuvant treatment of surgically resected breast cancer was evaluated in a meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG). The EBCTCG meta-analyses compared cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to no chemotherapy (19 trials including 7523 patients) and doxorubicin hydrochloride-containing regimens with CMF as an active control (6 trials including 3510 patients). Data from the meta- analysis of trials comparing CMF to no therapy were used to establish the historical treatment effect size for CMF regimens. The major efficacy outcome measures were disease-free survival (DFS) and overall survival (OS).

Of the 3510 women (2157 received doxorubicin hydrochloride-containing regimens and 1353 received CMF treatment) with early breast cancer involving axillary lymph nodes included in the six trials from the meta-analyses, approximately 70% were premenopausal and 30% were postmenopausal. At the time of the meta-analysis, 1745 first recurrences and 1348 deaths had occurred. The analyses demonstrated that doxorubicin hydrochloride-

containing regimens retained at least 75% of the historical CMF adjuvant effect on DFS with a hazard ratio (HR) of 0.91 (95% CI, 0.82–1.01) and on OS with a HR of 0.91 (95% CI, 0.81–1.03). Results of these analyses for both DFS and OS are provided in below table.

Table 2. Summary of Randomized Trials Comparing Doxorubicin hydrochloride - Containing Regimens versus CMF in Meta-Analysis

Study (starting year)	Regimens	No. of Cycles	No. of Patients	Doxorubicin hydrochloride-Containing Regimens vs. CMF HR*** (95% CI)	
				DFS	OS
NSABP B-15 (1984) SECSG 2 (1976) ONCOFRANCE (1978) SE Sweden BCG A (1980) NSABC Israel Br0283 (1983) Austrian BCSG 3 (1984)	AC CMF FAC CMF FACV CMF AC CMF AVbCMF* CMF CMFVA CMF	4 6 6 6 12 12 6 6 4 6 6 8	1562** 776 260 268 138 113 21 22 55 50 121 124	0.93 (0.82–1.06) 0.86 (0.66–1.13) 0.71 (0.49–1.03) 0.59 (0.22–1.61) 0.91 (0.53–1.57) 1.07 (0.73–1.55)	0.97 (0.83–1.12) 0.93 (0.69–1.26) 0.65 (0.44–0.96) 0.53 (0.21–1.37) 0.88 (0.47–1.63) 0.93 (0.64–1.35)
Combined Studies	Doxorubicin hydrochloride-Containing Regimens CMF		2157 1353	0.91 (0.82–1.01)	0.91 (0.81–1.03)

Abbreviations: DFS = disease free survival; OS = overall survival; AC = doxorubicin hydrochloride, cyclophosphamide; AVbCMF = doxorubicin hydrochloride, vinblastine, cyclophosphamide, methotrexate, 5- fluorouracil; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; CMFVA = cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, doxorubicin hydrochloride; FAC = 5-fluorouracil, doxorubicin hydrochloride,

cyclophosphamide; FACV = 5-fluorouracil, doxorubicin hydrochloride, cyclophosphamide, vincristine; HR = hazard ratio; CI = confidence interval

* Patients received alternating cycles of AVb and CMF.

** Includes pooled data from patients who received either AC alone for 4 cycles, or who were treated with AC for 4 cycles followed by 3 cycles of CMF.

*** A hazard ratio of less than 1 indicates that the treatment with doxorubicin hydrochloride-containing regimens is associated with lower risk of disease recurrences or death compared to the treatment with CMF.

5.2. Pharmacokinetic properties

Pharmacokinetic studies conducted in patients with various types of tumors have shown that doxorubicin follows multiphasic disposition after intravenous injection. The distribution half-life is approximately 5 minutes, while the terminal half-life is 20 to 48 hours. In four patients, doxorubicin demonstrated dose-independent pharmacokinetics across a dose range of 30 to 70 mg/m2.

Distribution

Steady-state distribution volume ranges from 809 to 1214 L/m2. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 75% and is independent of plasma concentration of doxorubicin up to 1.1 µg/mL.

Doxorubicin was measured in the milk of one lactating patient after therapy with 70 mg/m2 of doxorubicin hydrochloride given as a 15-minute intravenous infusion. The peak milk concentration at 24 hours after treatment was 4.4-fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours.

Doxorubicin does not cross the blood brain barrier.

Metabolism

Doxorubicin is a substrate of CYP3A4, CYP2D6, and P-gp.Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxic activity of doxorubicin hydrochloride. Disposition of doxorubicinol in patients is formation rate limited, with the terminal half-life of doxorubicinol being similar to doxorubicin. The relative exposure of doxorubicinol, i.e., the ratio between the AUC of doxorubicinol and the AUC of doxorubicin is approximately 0.5.

Elimination

Plasma clearance is in the range 324 to 809 mL/min/m2and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. In urine, <3% of the dose was recovered as doxorubicinol over 7 days. Systemic clearance of doxorubicin is significantly reduced in obese women with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight.

Pharmacokinetics in Special Populations

Pediatric patients

Following administration of doses ranging from 10 to 75 mg/m2 of doxorubicin hydrochloride to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 ± 114 mL/min/m2. Further analysis demonstrated that clearance in 52 children greater than 2 years of age (1540 mL/min/m2) was increased compared with adults. However, clearance in infants younger than 2 years of age (813 mL/min/m2) was decreased compared with older children and approached the range of clearance values determined in adults.

Patient Gender

There is no recommended dose adjustment based on gender. A published clinical study involving 6 men and 21 women with no prior anthracycline therapy reported a significantly higher median doxorubicin clearance in men compared to women (1088 mL/min/m2 versus 433 mL/min/m2). However, the terminal half-life of doxorubicin was longer in men compared to women (54 versus 35 hours).

Patients with hepatic impairment

The clearance of doxorubicin and doxorubicinol was reduced in patients with elevation in serum bilirubin.

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis and Impairment of Fertility

Doxorubicin hydrochloride treatment results in an increased risk of secondary malignancies. Doxorubicin hydrochloride was mutagenic in the *in vitro* Ames assay, and clastogenic in multiple *in vitro* assays (CHO cell, V79 hamster cell, human lymphoblast, and SCE assays) and the *in vivo* mouse micronucleus assay. Doxorubicin hydrochloride decreased fertility in female rats at the doses of 0.05 and 0.2 mg/kg/day (approximately 0.005 and 0.02 times the recommended human dose, based on body surface area).

A single intravenous dose of 0.1 mg/kg doxorubicin hydrochloride (approximately 0.01 times the recommended human dose based on body surface area) was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and oligospermia/hypospermia in rats. Doxorubicin hydrochloride induces DNA damage in rabbit spermatozoa and dominant lethal mutations in mice.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride USP
Hydrochloric Acid
USNF Water for
Injection USP

Incompatibilities

Do not admix doxorubicin hydrochloride with other drugs. If doxorubicin hydrochloride is mixed with heparin or fluorouracil a precipitate may form. Avoid contact with alkaline solutions which can lead to hydrolysis of doxorubicin hydrochloride.

6.3 Shelf-life

18 months

6.4 Special precautions for storage

Store under refrigeration 2°C – 8°C. Protect from light.

6.5 Nature and contents of container

ADRIM (Doxorubicin hydrochloride) is available as 5 ml and 25 ml vial containing 10 mg and 50 mg of Doxorubicin hydrochloride, respectively as a ready to use solution.

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate. However, given the toxic nature of this substance, the following protective recommendations are provided:

Personnel should be trained in good technique for reconstitution and handling.

Pregnant staff should be excluded from working with this drug.

Personnel handling doxorubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.

A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be 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 cleaning materials should be disposed of as indicated previously.

In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.

In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.

Always wash hands after removing gloves.

Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient's urine and other body fluids for at least 5 days after each treatment.

7.MARKETING AUTHORISATION HOLDER

Fresenius Kabi Oncology Limited:

Echelon Institutional area, Plot No 11, Sector 32, Gurgaon, 122001, Haryana, India

8.MARKETING AUTHORISATION NUMBER (S)

H99/016

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Not applicable

10. DATE OF REVISION OF THE TEXT:

14/06/2026