ADRIBLASTINA®
(Doxorubicin hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

ADRIBLASTINA®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Adriblastina Rapid Dissolution:

- 10 mg - each vial contains: Doxorubicin hydrochloride 10 mg (as a freeze dried powder with lactose and methylhydroxybenzoate).
- 50 mg - each vial contains: Doxorubicin hydrochloride 50 mg (as a freeze dried powder with lactose and methylhydroxybenzoate).

3. PHARMACEUTICAL FORM

- Sterile powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Doxorubicin is indicated in the treatment of the following cancers:

- acute lymphoblastic leukaemia[1,2,3]
- acute myelogenous leukaemia[4,5,6,7]
- chronic leukemias[8,9,10]
- Hodgkin's disease[7,11,12] & non-Hodgkin's lymphoma[7,13,14]
- multiple myeloma[15,16,17,18]
- osteosarcoma[19,20,21,22,23]
- Ewing's sarcoma[7,19,23]
- soft tissue sarcoma[23,24,25,26]
- neuroblastoma[27,28]
- rhabdomyosarcoma[29]
- Wilms' tumor[7,30,31,32]
- breast cancer,[7,33,34,35,36,37] including as a component of adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer[103]
- endometrial cancer[7,38,39,40,41]
- ovarian cancer[7,42,43]
- non-seminomatous testicular cancer[44,45]
- prostate cancer[46,47]
- transitional bladder cell cancer[48,49,50,51,52]
- lung cancer[53,54,55]
- stomach (gastric) cancer[56,57,58,59]

- primary hepatocellular cancer[60,61,62,63,64,65,66,67,68]
- head and neck cancer[69,70]
- thyroid cancer[71,72]

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Doxorubicin is usually administered by intravenous injection. Intravesical and intra-arterial routes may be used as indicated.

Intravenous (IV) 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.

Doxorubicin should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose solution) for not less than 3 minutes and not more than 10 minutes to minimize the risk of thrombosis or perivenous extravasation.[101,102] A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see section **4.4 Special warnings and precautions for use**).

Standard starting dose regimens. As a single agent, the recommended standard starting dose of doxorubicin per cycle in adults is 60-90 mg/m^2 of body surface area.[23,24,36,41,46,62,64,67,69,72] The total starting dose per cycle may be given as a single dose or divided over 3 successive days or given on days 1 and 8. Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), each treatment cycle could be repeated every 3 to 4 weeks. Administration of doxorubicin in a weekly regimen of 10-20 mg/m^2 has also been shown to be effective. If doxorubicin is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle is in the 30-60 mg/m^2 range.[5,6,9,10,11,22,24,25,27,30,37,38,41,44,45,49,54,58,61]

Adjuvant Therapy. In a large randomized study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-15 of patients with early breast cancer involving axillary lymph nodes, (see sections **4.8 Undesirable effects** and **5.1 Pharmacokinetic properties)** the combination dosage regimen of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) was administered intravenously on day 1 of each 21-day treatment cycle. Four cycles of treatment were administered.[104]

Dose Modifications

Hepatic Dysfunction. Dose reductions are recommended in patients with the following serum chemistry values:

- Bilirubin 1.2 to 3 mg/dL: ½ of recommended starting dose.
- Bilirubin >3 mg/dL: ¼ of recommended starting dose.

Doxorubicin should not be administered to patients with severe hepatic impairment (see section **4.3 Contraindications**).

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 (see section **4.4 Special warnings and precautions for use**).

Intravesical Administration[48,50,51]

Doxorubicin administered intravesically can be used for the treatment of superficial bladder tumors or as prophylaxis to reduce recurrence after trans-urethral resection. Intravesical administration is not suitable for the treatment of invasive tumors that have penetrated the muscular layer of the bladder wall.[116] Instillations of 30-50 mg in 25-50 mL of saline solution are recommended. In the case of local toxicity (chemical cystitis), the dose should be instilled in 50-100 mL of saline solution. Patients may continue to receive instillations in weekly to monthly intervals (see section **4.4 Special warnings and precautions for use**).

Doxorubicin should be instilled using a catheter and retained intravesically for 1 to 2 hours.[48] 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 undue 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.

Intra-arterial Administration[60,62,63,65,66,68]
Doxorubicin has been also used by the intra-arterial route in an attempt to produce intense local activity with reduced systemic toxicity in patients with hepatocellular carcinoma. Since this technique is potentially hazardous and can lead to widespread necrosis of the perfused tissue, intra-arterial administration should only be attempted by those physicians fully trained with this technique. Patients may receive an infusion into the main hepatic artery in doses of 30 to 150 mg/m^2 at intervals of 3 weeks to 3 months, with higher doses reserved for administration with concurrent extracorporeal drug elimination. Lower doses are suitable for administration of doxorubicin with iodized oil (see section **4.4 Special warnings and precautions for use**).

4.3 CONTRAINDICATIONS

Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones.

Intravenous (IV) use:
- persistent myelosuppression.
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (see section **4.4 Special warnings and precautions for use**).

Intravesical use:
- urinary infections
- inflammation of the bladder

- hematuria[117]

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Doxorubicin should be administered only under the supervision of physicians experienced in the use of cytotoxic therapy.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin.

The systemic clearance of doxorubicin is reduced in obese patients (i.e., >130% ideal body weight) (see section **4.2. Posology and method of administration**).[73]

Cardiac Function

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events.

Early (i.e., Acute) Events. Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for discontinuation of doxorubicin treatment.

Late (i.e., Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m^2, slowly increases up to the total cumulative dose of 450-550 mg/m^2. Thereafter, the risk of developing CHF increases steeply, and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2.[74,75,76]

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab). Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see section **4.5 Interaction with other medicinal products and other forms of interaction**). Patients receiving anthracyclines 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. The reported half-life of trastuzumab is variable. Trastuzumab may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.[120,125,126]

Cardiac function must be carefully monitored in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.[77,78]

Children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration. Females may be at greater risk than males. Follow-up cardiac evaluations are recommended periodically to monitor for this effect.[105,106,107,108,109,110]

It is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive.[79]

Hematologic Toxicity

As with other cytotoxic agents, doxorubicin may produce myelosuppression. Hematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

Secondary Leukemia

Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines (including doxorubicin).[111,112] Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiotherapy,[111,112] when patients have been heavily pretreated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1- to 3-year latency period.[27,80]

Gastrointestinal

Doxorubicin is emetigenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Hepatic Function

The major route of elimination of doxorubicin is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with doxorubicin. Patients with elevated bilirubin may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients (see section **4.2. Posology and method of administration**). Patients with severe hepatic impairment should not receive doxorubicin (see section **4.3 Contraindications**).

Effects at Site of Injection

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see section **4.2. Posology and method of administration**).

Extravasation

Extravasation of doxorubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of doxorubicin, the drug infusion should be immediately stopped.

Tumor-Lysis Syndrome

Doxorubicin may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumor-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.[121]

Other

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported. Radiation-induced toxicities (myocardium, mucosae, skin and liver) have also been reported.

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of doxorubicin.[87]

Additional Warnings and Precautions for Other Routes of Administration

Intravesical route. Administration of doxorubicin by the intravesical route may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., urethral obstruction due to massive intravesical tumors).

Intra-arterial route. Intra-arterial administration of doxorubicin (transcatheter arterial embolization) may be employed for the localized or regional therapy of primary hepatocellular carcinoma or liver metastases. Intra-arterial administration may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of doxorubicin) gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.[60,63,66,67]

Embryo-fetal Toxicity

Doxorubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with doxorubicin. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available (see sections **4.6. Fertility, pregnancy and lactation** and **5.3 Preclinical safety data**).[127]

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g., verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (e.g., phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin.[123]

The addition of cyclosporine to doxorubicin may result in increases in area under the concentration-time curve (AUC) for both doxorubicin and doxorubicinol, possibly due to a decrease in clearance of the parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of cyclosporin and doxorubicin.[123]

Doxorubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastrointestinal effects (see section **4.4. Special warnings and precautions for use**). 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.

Paclitaxel can cause increased plasma-concentrations of doxorubicin and/or its metabolites when given prior to doxorubicin. Certain data indicate that this effect is minor when anthracycline is administrated prior to paclitaxel.[118]

Both increases (21% - 47%) and no change in the AUC of doxorubicin were observed with concomitant treatment with sorafenib 400 mg twice daily. The clinical significance of these findings is unknown.[122]

4.6. FERTILITY, PREGNANCY AND LACTATION

(see also section **5.3 Preclinical safety data**)

Impairment of Fertility

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.[83,84]

In men, 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.[85,86] Both men and women should seek advice on fertility preservation before treatment.[127]

Pregnancy

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.[88,89,90,91,92,93]

Doxorubicin has been implicated in causing fetal harm when administered to a pregnant woman.[94] If a woman receives doxorubicin during pregnancy or becomes pregnant while taking the drug, she should be apprised of the potential hazard to the fetus.

Women of Childbearing Potential/Contraception in Males and Females

Women of childbearing potential should be advised to avoid becoming pregnant during treatment and to use effective contraceptive methods during treatment and for at least 6 months and 10 days after last dose.[127] Men with female partners of childbearing potential should be advised to use effective contraception during treatment with doxorubicin and for at least 3 months and 10 days after last dose.[127]

Lactation

Doxorubicin is excreted in breast milk (see section **5.2. Pharmacokinetic properties**). Because of the potential for serious reactions in nursing infants from doxorubicin women should not breastfeed while undergoing treatment with doxorubicin and for at least 10 days after last dose.[95,96,127]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of doxorubicin on the ability to drive or use machinery has not been systematically evaluated.

4.8. UNDESIRABLE EFFECTS

Adverse reactions reported in association with doxorubicin therapy are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common (≥10%), Common (≥1%, <10%), Uncommon (≥0.1%, <1%), Rare (≥0.01%, <0.1%), Very rare (<0.01%), and Not known (cannot be estimated from available data).[124]

Adverse Reactions Table

Infections and Infestations	
Very common	Infection
Common	Sepsis
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	
Not known	Acute lymphocytic leukaemia, Acute myeloid leukaemia
Blood and Lymphatic System Disorders	
Very common	Leukopenia, Neutropenia, Anaemia, Thrombocytopenia
Immune System Disorders	
Not known	Anaphylactic reaction
Metabolism and Nutrition Disorders	
Very common	Decreased appetite
Not known	Dehydration, Hyperuricaemia
Eye Disorders	
Common	Conjunctivitis
Not known	Keratitis, Lacrimation increased
Cardiac Disorders	
Common	Cardiac failure congestive, Sinus tachycardia
Not known	Atrioventricular block, Tachyarrhythmia, Bundle branch block
Vascular Disorders	
Uncommon	Embolism
Not known	Shock, Haemorrhage, Thrombophlebitis, Phlebitis, Hot flush

Gastrointestinal Disorders	
Very common	Mucosal inflammation/Stomatitis, Diarrhoea, Vomiting, Nausea
Common	Oesophagitis, Abdominal pain
Not known	Gastrointestinal haemorrhage, Gastritis erosive, Colitis, Mucosal discolouration
Skin and Subcutaneous Tissue Disorders	
Very common	Palmar-plantar erythrodysaesthesia syndrome[113] Alopecia
Common	Urticaria, Rash, Skin hyperpigmentation, Nail hyperpigmentation
Not known	Photosensitivity reaction, Recall phenomenon, Pruritus, Skin disorder
Renal and Urinary Disorders	
Not known	Chromaturia[a]
Reproductive System and Breast Disorders	
Not known	Amenorrhoea, Azoospermia, Oligospermia
General Disorders and Administration Site Conditions	
Very common	Pyrexia, Asthenia, Chills
Common	Infusion site reaction
Not known	Malaise
Investigations	
Very common	Ejection fraction decreased, Electrocardiogram abnormal, Transaminases abnormal, Weight increased[b, 104]

[a]For one to two days after administration.
[b]Reported in patients with early breast cancer receiving doxorubicin-containing adjuvant therapy (NSABP B-15 trial).[104]

4.9. OVERDOSE

Acute overdosage with doxorubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac alterations.[119]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

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.

Clinical Studies

The effectiveness of doxorubicin-containing regimens in the adjuvant therapy of early breast cancer has primarily been established based on data collected in a meta-analysis published in 1998 by the Early Breast Cancer Trialists Collaborative Group (EBCTCG). The EBCTCG obtains primary data on all relevant studies, both published and unpublished, for early stage breast cancer and regularly updates these analyses. The principal endpoints for the adjuvant chemotherapy trials were disease-free survival (DFS) and overall survival (OS). The meta-analyses allowed comparisons of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to no chemotherapy (19 trials including 7523 patients) and comparisons of doxorubicin-containing regimens with CMF as an active control (6 trials including 3510 patients). The pooled estimates of DFS and OS from these trials were used to calculate the effect of CMF relative to no therapy. The hazard ratio for DFS for CMF compared to no chemotherapy was 0.76 (95% CI 0.71-0.82) and for OS was 0.86 (95% CI 0.80-0.93). Based on a conservative estimate of CMF effect (lower 2-sided 95% confidence limit of hazard ratio) and 75% retention of CMF effect on DFS, it was determined that the doxorubicin containing-regimens would be considered as non-inferior to CMF if the upper 2-sided 95% confidence limit of the hazard ratio was less than 1.06, i.e., not more than 6% worse than CMF. A similar calculation for OS would require a non-inferiority margin of 1.02.[103]

Six randomized trials in the EBCTCG meta-analysis compared doxorubicin-containing regimens to CMF. A total of 3510 women with early breast cancer involving axillary lymph nodes were evaluated; approximately 70% were premenopausal and 30% were post-menopausal. At the time of the meta-analysis, 1745 first recurrences and 1348 deaths had occurred. Analyses demonstrated that doxorubicin-containing regimens retained at least 75% of the historical CMF adjuvant effect on DFS and are effective. The hazard ratio for DFS (dox: CMF) was 0.91 (95% CI 0.82-1.01) and for OS was 0.91 (95% CI 0.81-1.03).[103]

The largest of the 6 studies in the EBCTCG meta-analysis, a randomized, open-label, multicenter trial (NSABP B-15) was conducted in approximately 2300 women (80% premenopausal; 20% post-menopausal) with early breast cancer involving axillary lymph nodes. In this trial, 6 cycles of conventional CMF was compared to 4 cycles of doxorubicin and cyclophosphamide (AC) and 4 cycles of AC followed by 3 cycles of CMF. No statistically significant differences in terms of DFS or OS were observed.[104]

5.2. PHARMACOKINETIC PROPERTIES

Distribution

The initial distribution half-life of approximately 5 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volume ranges from 809 to 1214 L/m^2 and is indicative of extensive drug uptake into tissues. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin up to 1.1 µg/mL.

Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration at 24 hours after treatment being approximately 4.4-fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy with 70 mg/m^2 of doxorubicin given as a 15-minute intravenous infusion and 100 mg/m^2 of cisplatin as a 26-hour intravenous infusion. The peak concentration of doxorubicinol in milk at 24 hours was 0.11 µg/mL and AUC up to 24 hours was 9.0 µg.h/mL while the AUC for doxorubicin was 5.4 µg.h/mL.

Doxorubicin does not cross the blood brain barrier.

Metabolism

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. Disposition of doxorubicinol (DOX-OL) in patients is formation rate limited, with the terminal half-life of DOX-OL being similar to doxorubicin. The relative exposure of DOX-OL, i.e., the ratio between the AUC of DOX-OL and the AUC of doxorubicin, compared to doxorubicin ranges between 0.4 and 0.6.

Excretion

Plasma clearance is in the range 324 to 809 mL/min/m^2 and is predominantly 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 DOX-OL 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 (see section **4.2. Posology and method of administration**).

Pharmacokinetics in Special Populations

Pediatric. Following administration of 10 to 75-mg/m^2 doses of doxorubicin to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 ± 114 mL/min/m^2. Further analysis demonstrated that clearance in 52 children greater than 2 years of age (1540 mL/min/m^2) was increased compared with adults. However, clearance in infants younger than 2 years of age (813 mL/min/m^2) was decreased compared with older children and approached the range of clearance values determined in adults (see sections **4.2. Posology and method of administration** and **4.4 Special warnings and precautions for use**).

Geriatric. While the pharmacokinetics of elderly subjects (≥65 years of age) have been evaluated, no dosage adjustment is recommended based on age.

Gender. A published clinical study involving 6 men and 21 women with no prior anthracycline therapy reported a significantly higher median doxorubicin clearance in the men compared to the women (1088 mL/min/m^2 versus 433 mL/min/m^2). However, the terminal half-life of doxorubicin was longer in men compared to the women (54 versus 35 hours).[114]

Race. The influence of race on the pharmacokinetics of doxorubicin has not been evaluated.

Hepatic Impairment. The clearance of doxorubicin and doxorubicinol was reduced in patients with impaired hepatic function (see section **4.2. Posology and method of administration**).

Renal Impairment. The influence of renal function on the pharmacokinetics of doxorubicin has not been evaluated.

5.3. PRECLINICAL SAFETY DATA

Carcinogenesis & Mutagenesis

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.[81,82]

Impairment of Fertility

Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia.[81,82]

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lactose & Methyl Hydroxybenzoate.

6.2. INCOMPATIBILITIES

Doxorubicin should not be mixed with other drugs.[100] 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.

Doxorubicin should not be mixed with fluorouracil (e.g., in the same IV infusion bag or at the Y-site of an IV infusion line) since it has been reported that these drugs are incompatible to the extent that a precipitate might form. If concomitant therapy with doxorubicin and fluorouracil is required, it is recommended that the IV line be flushed between the administration of these drugs.[123]

6.3. SHELF LIFE

Please see pack for expiry of product.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15 - 25°C).[115]

6.5. NATURE AND CONTENTS OF CONTAINER

ADRIBLASTINA® (doxorubicin) is available with the following presentations.

Adriblastina Rapid Dissolution:

Box of 1 x 10 mg vial + 5 mL diluent for reconstitution

Box of 1 x 50 mg vial

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation of the freeze-dried powder for intravenous administration

Dissolve powder in sodium chloride/water for injection. The vial contents are under negative pressure. To minimize aerosol formation during reconstitution; particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided.

Protective measures

The following protective recommendations are given due to the toxic nature of this substance:

- 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.

Adriblastina/LPD/PK-04
According to CDS V 11 dated September 10, 2021; Supersedes CDS V 10 dated: November 21, 2018

Marketed by:
Pfizer Pakistan Limited
Please visit our website ***www.pfizerpro.com.pk*** *for latest version of Product leaflet.*

7 REFERENCES

1. Tanimoto M, Miyawaki S, Ino T, et al. Response-oriented individualized induction therapy followed by intensive consolidation and maintenance for adult patients with acute lymphoblastic leukemia: the ALL-87 study of the Japan Adult Acute Leukemia Study Group (JALSG). Intl J. Hematol. 1998; 68:421-429.

2. Bassan R, Lerede T, Rambaldi A, Barbui T. Role of anthracyclines in the treatment of adult acute lymphoblastic leukemia. Acta Haematol 1996;95(3-4):188-192.

3. Sallan SE, Gelber RD, Kimball V, Donnelly M, Cohen HJ. More is better: update of Dana-Farber Cancer Institute/Children's Hospital childhood acute lymphoblastic leukemia trials. Haematol. Bluttransf. 1990;33: 459-466.

4. Bessho F, Kigasawa H, Tsuchida M, et al. Improved prognosis of acute nonlymphocytic leukemia in children: results of the 12th ANLL protocol of Tokyo Children's Cancer Study Group. Acta Paediatr.Jap. 1991; 33: 533-9.

5. Krischer JP, Steuber CP, Vietti TJ, et al. Long-term results in the treatment of acute nonlymphocytic leukemia: a Pediatric Oncology Group Study. Med Pediatr Oncol 1989; 7:401-408.

6. Van der Does-van der Berg A, Hhlen K, Colly LP, Vossen J.M. Treatment of childhood acute nonlymphocytic leukemia with high-dose cytosine arabinoside, 6-thioguanine, and doxorubicin without maintenance therapy: pilot study ANLL-80 of the Dutch Childhood Leukemia Study Group (DCLSG). Pediatr Hematol Oncol 1988; 5:93-102.

7. Bonadonna G. Present Role of Doxorubicin (Adriamycin) in the treatment of neoplastic disease. Clin Trials J 1987;24(1), 3-10.

8. Foon KA, Gale RP. Staging and therapy of chronic lymphocytic leukemia. Semin Hematol 1987; 24:264-274.

9. Walters RS, Kantarjian HM, Keating MJ, et al. Therapy of lymphoid and undifferentiated chronic myelogenous leukemia in blast crisis with continuous vincristine and adriamycin infusion plus high-dose decadron. Cancer 1987; 60:1708-1712.

10. French Cooperative Group on Chronic Lymphocytic Leukaemia. Effectiveness of “CHOP” regimen in advanced untreated chronic lymphocytic leukaemia. Lancet 1986; 1(No. 8494):1346-1349.

11. Aisenberg AC. Problems in Hodgkin’s disease management. Blood 1999;93(3):761-779.

12. Bonfante V, Santoro A, Viviani S, et al. ABVD in the treatment of Hodgkin's disease. Semin Oncol 1992;19(S5):38-44.

13. Martelli M, DeSanctis V, Avvisati G, Mandelli F. Current guidelines for the management of aggressive non-Hodgkin's lymphoma. Drugs 1997;53(6):957-972.

14. Fisher RI. Treatment of aggressive non-Hodgkin lymphomas. Lessons from the past 10 years. Cancer 1994;74(s9):2657-2561.

15. Segeren CM, Sonneveld P, van der Holt B, et al. Vincristine, doxorubicin and dexamethasone (VAD) administered as rapid intravenous infusion for first-line treatment in untreated multiple myeloma. Br J Haematol 1999;105(1):127-130.

16. Alexanian R, Dimopoulos M. The treatment of multiple myeloma. N Engl J Med 1994;330(7):484-489.

17. MacLennan IC, Drayson M, Dunn J. Multiple myeloma. BMJ 1994;308:1033-1036.

18. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med 1984;310:1353-1356.

19. Sæter G, Alvegå TA, Elomaa I, et.al. Chemotherapy for osteosarcoma and Ewing's sarcoma. Acta Orthop Scand 1997;68(273):120-125.

20. Womer RB. Problems and controversies in the management of childhood sarcomas. Br. Med. Bull. 1996;52:826-843.

21. Jaffe N, Patel SR, Benjamin RS. Chemotherapy in osteosarcoma. Basis for application and antagonism to implementation; early controversies surrounding its implementation. Hematol Oncol Clin North Am 1995;9(4):825-840.

22. Blaney SM, Smith MA, Grem JL. Doxorubicin: role in the treatment of osteosarcoma. In Osteosarcoma in adolescents and young adults: new developments and controversies. Eds. Humphrey GB, Koops HS, Molenaar WM, Postma A. Kluwer Academic Publishers 1993; Chapter 10;55-73.

23. Antman KH. Chemotherapy of advanced sarcomas of bone and soft tissue. Semin Oncol 1992;19(S6):13-20.

24. Rouesse J, Spielmann M, Le Chevalier T, et al. Chemotherapy of soft tissue sarcoma in adults. Bull Acad Natl Med 1991;175(8):1251-1260. [English Abstract]

25. Sawyer M, Bramwell V. The treatment of distant metastases in soft tissue sarcoma. Semin Radiat Oncol 1999;9(4):389-400.

26. Zalupski MM, Baker LH. Systemic adjuvant chemotherapy for soft tissue sarcomas. Hematol Oncol Clin North Am 1995;9(4):787-800.

27. Kushner BH, Cheung NK, Kramer K, et al. Neuroblastoma and treatment-related myelodysplasia/leukemia: the Memorial Sloan-Kettering experience and a literature review. J Clin Oncol 1998;16(12).

28. Cheung NV, Heller G. Chemotherapy dose intensity correlates strongly with response, median survival, and median progression-free survival in metastatic neuroblastoma. J Clin Oncol 1991;9(6):1050-1058.

29. Hays DM. Rhabdomyosarcoma. Clin Orthop Rel Res 1993;(289):36-49.

30. Neville HL, Ritchey ML. Wilms' tumor Overview of National Wilms' Tumor Study Group results. Urologic Clin North Am 2000;27(3):435-442.

31. Mehta MP, Bastin KT, Wiersma SR. Treatment of Wilms' tumour. Current recommendations. Drugs 1991;42(5):766-780.

32. National Wilms' Tumor Study Committee. Wilms' tumor: status report, 1990. J Clin Oncol 1991;9:877-887.

33. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Can Med Assoc J 1998;158(3):S52-S64.

34. Hudis CA, Norton L. Adjuvant drug therapy for operable breast cancer. Seminars in Oncology 1996;23(4):475-493.

35. Wiseman CL. Inflammatory breast cancer: 10-year follow-up of a trial of surgery, chemotherapy, and allogeneic tumor cell/BCG immunotherapy. Cancer Invest. 1995;13: 267-271.

36. Clavel M, Catimel G, Breast cancer: chemotherapy in the treatment of advanced disease. Eur J Cancer 1993;29a(4):598-604.

37. Namer M. Anthracyclines in the adjuvant treatment of breast cancer. Drugs 1993;45(2):4-9.

38. Pustilnic T, Burke TW. Adjuvant chemotherapy for high-risk endometrial cancer. Semin Radiat Oncol 2000;10(1):23-28.

39. Chen LM, McGonigle KF, Berek JS. Endometrial cancer: recent developments in evaluation and treatment. Oncology 1999;13(12):1665-1670.

40. Fehr MK, Wight E, Haller U. Chemotherapy of endometrial cancer revisited. Gynäkol Geburtshilfliche Rundsch 1999;39:110-120. [English Abstract]

41. Moore TD, Phillips PH, Nerenstone SR, Cheson BD. Systemic treatment of advanced and recurrent endometrial carcinoma: current status and future directions. J Clin Oncol 1991;9(6):1071-1088

42. A'Hern RP, Gore ME. Impact of doxorubicin on survival in advanced ovarian cancer. J Clin Oncol 1995;13: 726-32.

43. Vermorken JB, Harper PG, Buyse M. The role of anthracyclines in epithelial ovarian cancer. Ann Oncol 1999;10(1):43-50.

44. Lederman GS, Garnick MB. Possible benefit of doxorubicin treatment in patients with refractory germ cell cancer. Cancer 1986;58(11):2393-2398.

45. Logothetis CJ, Samuels ML, Selig DE, et al. Cyclic chemotherapy with cyclophosphamide, doxorubicin and cisplatin plus vinblastine and bleomycin in advanced germinal tumors. Results with 100 patients. Am J Med 1986;81(2):219-28.

46. Beedassy A, Cardi G. Chemotherapy in advanced prostate cancer. Semin Oncol 1999;26(4):428-438.

47. Ellerhorst JA, Tu SM, Amato RJ, et al. Phase II trial of alternating weekly chemohormonal therapy for patients with androgen-independent prostate cancer. Clin Cancer Res 1997; 3: 2371-2376.

48. Duque JLF, Loughlin KR. Superficial bladder cancer: new strategies in diagnosis and treatment. Urol Clin North Am 2000;27(1):125-135.

49. Antoine ED, Khayat D. The role of new drugs in the treatment of locally advanced urothelial tumors of the bladder. Cancer Radiother 1998;2(S1):97s-102s. [English abstract]

50. Kurth K, Tunn U, Ay R, et al. Adjuvant chemotherapy for superficial transitional cell bladder carcinoma: Long-term results of a European Organization for Research and Treatment of Cancer randomized trial comparing doxorubicin, ethoglucid and transurethral resection alone. J Urol 1997;158(2):378-384.

51. DeReijke TM, Kurth K. Doxorubicin and epirubicin. In: Superficial Bladder Cancer. eds. Pagano F, Fair WR. Oxford, UK: Isis Medical Media Ltd. 1997:97-106.

52. Roth BJ, Bajorin DF. Advanced bladder cancer: the need to identify new agents in the post-M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) world. J Urol 1995;153(3s):894-900.

53. Bitran JD, Vokes EE. Chemotherapy for stage IV non-small cell lung cancer. Hematol Oncol Clin NA 1990; 4:1159-1168.

54. Saijo N. Combined modality therapy for small cell lung cancer. Oncology 1992;49(s1):2-10.

55. Sandler AB, Buzaid AC. Lung cancer: a review of current therapeutic modalities. Lung 1992;170(5):249-265.

56. Klein HO. Neo-adjuvants, adjuvants and palliative therapy for gastric carcinoma. Schweiz Rundsch Med Prax 1998;87 13:451-454. [English abstract].

57. Hendlisz A, Bleiberg H. Diagnosis and treatment of gastric cancer. Drugs 1995;49(5):711-720.

58. Roth AD, Herrmann R, Morant R, et al. Cisplatin, doxorubicin and etoposide (PAV) in advanced gastric carcinoma: the SAKK experience. Swiss Group for Clinical Cancer Research (SAKK). Eur J Cancer 1998;34(13):2126-2128.

59. Schipper DL, Wagener DJ. Chemotherapy of gastric cancer. Anticancer Drugs. 1996;7(2):137-149.

60. Acunaş B, Rozanes I. Hepatocellular carcinoma: treatment with transcatheter arterial chemoembolization. Eur J Radiol 1999;32(1):86-89.

61. Leung TWT, Patt YZ, Lay WY, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res 1999;5:1676-1681.

62. Tzoracoleftherakis EE, Spiliotis JD, Kyriakopoulou T, Kakkos SK. Intra-arterial versus systemic chemotherapy for non-operable hepatocellular carcinoma. Hepato-Gastroenterology, 1999;46(26):1122-1125.

63. Ku Y, Iwasaki T, Fukumoto T, et al. Induction of long-term remission in advanced hepatocellular carcinoma with percutaneous isolated liver chemoperfusion. Ann Surg 1998;227(4):519-526.

64. Johnson PJ, Dobbs N, Kalayci C. Clinical efficacy and toxicity of standard dose adriamycin in hyperbilirubinemic patients with hepatocellular carcinoma: relation to liver tests and pharmacokinetic parameters. Br J Cancer 1992; 65:751-5.

65. Nonami T, Isshiki K, Katoh H, Kishimoto W, Harada A, Nakao A, et al. The potential role of postoperative hepatic artery chemotherapy in patients with high-risk hepatomas. Ann Surg 1991;213(3):222-6.

66. Doci R, Bignami P, Bozzetti F, et al. Intrahepatic chemotherapy for unresectable hepatocellular carcinoma. Cancer 1988;61:1983-1987.

67. Nerenstone S, Friedman M. Medical treatment of hepatocellular carcinoma. Gastroenterol Clin North Am 1987;16(4):603-612.

68. Yamakado K, et al. Long-term follow-up arterial chemobolization combined with transportal ethanol injection used to treat hepatocellular carcinoma. JVIR 1999;10(5):641-647.

69. Cobleigh MA, Hill JH, Gallagher PA, et al. A phase II study of Adriamycin in previously untreated squamous cell carcinoma of the head and neck. Cancer 1985;56(11):2573-2575.

70. Creagan ET, O'Fallon JR, Schutt AJ, et al. Cyclophosphamide, Adriamycin, and 24-hour infusion of cis-diamminedichloroplatinum (II) in the management of patients with advanced head and neck neoplasms Head & Neck Surg 1984;6:738-43.

71. Austin JR, el-Naggar AK, Goepfert H. Thyroid cancers. II Medullary, anaplastic, lymphoma, sarcoma, squamous cell. Otolaryngol Clin North Am 1996;29(4):611-627.

72. Ekman ET, Lundell G, Tennvall J, Wallin G. Chemotherapy and multimodality treatment in thyroid carcinoma. Otolaryngol Clin North Am 1990;23(3):523-527.

73. Rodvold KA, Rushing DA, Tewksbury DA. Doxorubicin clearance in the obese. J Clin Oncol 1988;6(8):1321-1327.

74. Wang SQ. Electrocardiogram analysis of Adriamycin cardiotoxicity in 160 cases. Chin J Oncol 1991; 13:71-73.

75. Jain D. Cardiotoxicity of doxorubicin and other anthracycline derivatives. J. Nucl. Cardiol. 2000; 7: 53-62.

76. Bielack SS, Erttmann R, Kempf-Bielack B, Winkler K. Impact of scheduling on toxicity and clinical efficacy of doxorubicin: what do we know in the mid-nineties? Eur J Cancer 1996;32A(10):1652-1660.

77. Steinherz LJ, Steinherz PG, Tan CTC, et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991; 266:1672-1677.

78. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults. Semin. Oncol. 1998; 25 (Suppl. 10): 72-85.

79. Lebwohl DE, Canetta R. New developments in chemotherapy of advanced breast cancer. Ann. Oncol. 1999; 10 (Suppl. 6): 139-46.

80. Downing JR, Look AT. MLL fusion genes in the 11q23 acute leukemias. In: Molecular Genetics and Therapy of Leukemia, eds. EJ Freireich & H Kantarjian. Kluwer Acad., Norwell, Mass., 1996, pp. 73-92.

81. Mazué G, Williams GM, Iatropoulos MJ, et al. Anthracyclines: Review of genotoxicity and carcinogenicity studies. Int J Oncol 1996;8:525-536.

82. Mazué G, Iatropoulos M, Imondi A, et al. Anthracyclines: A review of general and special toxicity studies. Int J Oncol 1995; 7:713-726.

83. Sutton R, Buzdar AU, Hortobagyi GNB. Pregnancy and offspring after adjuvant chemotherapy in breast cancer patients. Cancer 1990; 65:847-50.

84. Falkson G, Gelman RS, Torney DC, et al. The ECOG experience with cyclophosphamide, adriamycin, and 5-fluorouracil (CAF) in patients with metastatic breast cancer. Cancer 1985;56(2):219-24.

85. Da Cunha MF, Meistrich ML, Ried HL, et al. Active sperm production after cancer chemotherapy with doxorubicin. J Urol 1983;130(5):927-930.

86. Pryzant RM, Meistrich ML, Wilson G, et al. Long-term reduction in sperm count after chemotherapy with and without radiation therapy for non-Hodgkin's lymphomas. J Clin Oncol 1993;11(2):239-247.

87. Bauer KA, Levine M. Evaluation and management of the cancer patient with thrombosis. In: American Society of Clinical Oncology (ASCO) Educational Book. 223-233, 1999.

88. Bertazzoli C, Rallo F. Adriamycin – Effect on fertility and reproduction in female rats treated intravenously. Farmitalia Carlo Erba; 1977 Jun. Report No. DOXO/445i.

89. Bertazzoli C. Adriamycin – Teratological study in rats (intravenous administration). Farmitalia Carlo Erba;1977 Sept. Report No. DOXO/446i.

90. Merei J, Hastorpe S, Farmer P, Hutson J.M. Visceral anomalies in prenatally adriamycin-exposed rat fetuses: A model for the VATER association. Pediatr Surg Int 1999; 15:11-16.

91. Kotsios C, Merei J, Hutson JM, Graham HK. Skeletal anomalies in the adriamycin-exposed prenatal rat: A model for VATER association. J Orthop Res 1998;16(1):50-53.

92. Menegola E, Broccia ML, Prati M, et al. Comparative embryotoxicity of four anthracyclines: In vitro study on their effects on glutathione status. Toxicol In vitro 1997;11(1-2):33-41.

93. Bertazzoli C. Adriamycin—Teratological study in rabbits (i.v. administration). Farmitalia Carlo Erba;1977 Sept: Report No. DOXO/447i.

94. Artlich A, Moller J, Tschakaloff A, et al. Teratogenic effects in a case of maternal treatment for acute myelocytic leukemia-- neonatal and infantile course. Eur.J.Pediatr 1994;153:488-91.

95. Egan PC, Costanza ME, Dodion P, et al. Doxorubicin and cisplatin excretion into human milk. Cancer Treat Rep 1985;69(12):1387-1389.

96. Riggs CE, Bachur NR. Clinical pharmacokinetics of anthracycline antibiotics. In: Pharmacokinetics of Anticancer Agents in Humans, eds. Ames MM, Powis G, Kovach JS. Elsevier Science Publishers B.V. Amsterdam, Netherlands. pp 229-278, 1983.

100. Galassi A, Hubbard SM, Alexander HR, Steinhaus E. Chemotherapy administration: practical guidelines. In: Cancer Chemotherapy and Biotherapy, 2nd Edition, eds. Chabner BA and Longo DL. Lippincott-Raven, Philadelphia, Pa. pp. 529-51, 1996.

101. AHFS Drug Information. Antineoplastic agents - doxorubicin hydrochloride. 2000, pp 913.

102. Dorr RT, Alberts DS. Pharmacology of doxorubicin. In Current Concepts in the Use of Doxorubicin Chemotherapy. ed. SE Jones, 1982.

103. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998; 352:930-42.

104. Fisher B, Brown AM, Nikolay V, et al: Two Months of Doxorubicin-Cyclophosphamide With and Without Interval Reinduction Therapy Compared with 6 Months of Cyclophosphamide, Methotrexate, and Fluorouracil in Positive-Node Breast Cancer Patients with Tamoxifen-Nonresponsive Tumors: Results From the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990; 8:1483-96.

105. Pein F, Sakiroglu O, Dahan M, et al: Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of solid tumour at the Institut Gustave Roussy. Brit J of Cancer 2004; 91: 37-44.

106. Kremer LCM, van Dalen EC, Offringa J, et al: Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. J Clin Oncol 2001; 19(1): 191-96.

107. Kesavan S, Lincoff MA, Young, JB: Anthracycline-induced cardiotoxicity. Ann of Inter Med 1996; 125(1): 47-58.

108. Green DM, Yevgeny A, Grigoriev, BN, et al: Congestive Heart Failure After Treatment for Wilms' Tumor: A Report From The National Wilms' Tumor Study Group. J Clin Oncol 2001; 19(7): 1926-34.

109. Lipshultz SE, Lipsitz SR, Mone SM, et al: Female sex and higher drug dose risk for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Eng J Med 1995; 332: 1738-43.

110. Silber JH, Jakacki RI, Larse RL, et al: Increased risk of cardiac dysfunction after anthracyclines in girls. Med Pediatr Oncol 1993; 21:477-79.

111. Smith RE, Bryant J, DeCillis A, et al: Acute Myeloid Leukemia and Myelodysplastic Syndrome after Doxorubicin-Cyclophosphamide Adjuvant Therapy for Operable Breast Cancer: The National Surgical Adjuvant Breast and Bowel Project Experience. J Clin Oncol 2003; 21(7): 1195-1204.

112. Diamandidou E, Buzdar AU, Smith TL, et al: Treatment-related leukemia in breast cancer patients treated with fluorouracil-doxorubicin-cyclophosphamide combination adjuvant chemotherapy: the University of Texas M.D. Anderson Cancer Center experience. J Clin Oncol 1996; 14(10): 2722-30.

113. Rogers D. Clinical Expert Statement for Doxorubicin and the Adverse Event Palmar Plantar Erythrodysaesthesia, 26 November 2003.

114. Dobbs NA, Twelves CJ, Gillies H, et al: Gender affects doxorubicin pharmacokinetics in patients with normal liver biochemistry. Cancer Chemother Pharmacol 1995 36: 473-76.

115. Colombo G. Viscosity change with temperature of Doxorubicin Hydrochloride Injection. November 2003 - In-house study (PNU-108112A) d0624092.

116. Marini, G. and Prescott, H. Clinical Expert Statement on Intravesical Administration for Invasive Bladder Tumors, dated 10 March 2006 Pfizer Inc.

117. Marini, G. Clinical Expert Statement on Contraindications for Doxorubicin Intravesical Administration in Patients with Superficial Bladder Tumours and Hematuria, dated 22 March 2006 Pfizer Inc.

118. Dychter, S. and Racanelli, T. Clinical Expert Report Evaluation of Pharmacokinetic Interaction between Doxorubicin and Paclitaxel, dated 23 March 2006 Pfizer Inc.

119. Marini G. *Clinical Expert Statement on Doxorubicin Overdose*, dated 14 November 2005, Pfizer Inc.

120. Lincoff A, Puccio D. A Clinical Expert Report to support revisions to the Core Data Sheet for Anthracyclines. Safety & Risk Management, Pfizer Inc. October 2008.

121. Lincoff A, Racanelli T. A Clinical Expert Report to support revisions to the doxorubicin Core Data Sheet. Safety & Risk Management, Pfizer Inc. October 2008.

122. Lincoff A, Vo T. Clinical Overview to support revisions to the doxorubicin Core Data Sheet. Safety & Risk Management, Pfizer Inc. August 2009

123. 2.5. Clinical Overview to support revisions to the doxorubicin Core Data Sheet, AUG-2011.

124. Module 2.5 ADR Frequency and Category Clinical Overview. September 2013.

125. 2.5. Clinical Overview to support revisions to the doxorubicin Core Data Sheet, February 2014.

126. 2.5 Clinical Overview Update to section 4.4 Special Warnings and Precautions for Doxorubicin HCl Core Data Sheet, October 2018.

127. 2.5 Clinical Overview to Support the Updates to Section 4.4 Special Warnings and Precautions for Use and Section 4.6 Fertility, Pregnancy and Lactation of the Core Data Sheet, August 2021.