Summary of Product Characteristics

1. Name of the medicinal product:

I-Dox 20mg/10ml

2. Qualitative and quantitative composition

Each ml contains

Doxorubicin Hydrochloride USP 2mg (As pegylated Liposome)

Water for Injection USP q. s.

3. Pharmaceutical form

Liquid Injection

4. Clinical particulars

4.1 Therapeutic indications

Antimitotic and cytotoxic. Doxorubicin has been used with success to produce regression in a wide range of neoplastic conditions including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours, in particular of breast and lung. Doxorubicin can be used in the treatment of non-metastatic transitional cell carcinoma, carcinoma in situ and papillary tumours of the bladder, by intravesical administration.

Doxorubicin is frequently used in combination chemotherapy regimens with other cytostatic drugs.

4.2 Posology and method of administration

Each 10 ml contains 20 mg of Doxorubicin HCl respectively at a concentration of 2 mg/ml.

Preparation for Intravenous Administration: A maximum dose of 90 mg diluted in 250 ml of 5 % Dextrose injection IP / USP prior to administration is the most appropriate dose of I-dox®. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is incorporated in the preparation of i-dox®. Diluted i-dox® should be refrigerated between 2-8 °C (36-46 °F) and administered within 24 hours.

Diluted preparation of I-dox® for intravenous administration should not be used with in line filters nor used with any diluent other than 5 % dextrose injection and, should not be used with any bacteriostatic agent such as benzyl alcohol. I-dox® is an unclear translucent, red liposomal dispersion. I-dox® should be

visually inspected for particulate matter and discoloration prior to administration and should not be used if precipitate or foreign matter is present.

It is strictly recommended that I-dox® should not be mixed with other drugs as HCl liposome injection is considered to be an irritant and necessary precautions should be taken to avoid extravasation. Extravasation may occur with or without an accompanying stinging or burning sensation on intravenous administration of i-dox® even if blood returns well on aspiration of the infusion needle. Infusion should be promptly terminated if any signs or symptoms of extravasation are seen and restarted in another vein. The application of ice over the site of extravasation for around 30 minutes may be helpful to alleviate local reaction.

I-dox® should not be given by intramuscular or subcutaneous route.

In general, Doxorubicin HCl liposome injection should not be administered as a bolus injection or as an undiluted solution. Rapid infusion may attenuate the risk of infusion-related reactions.

In ovarian cancer patients, Doxorubicin HCl liposome injection should be administered intravenously with an initial rate of 1 mg/min and a (Doxorubicin HCl equivalent) dose of 50 mg/m^2 minimize the risk of infusion reactions. If no infusion related AE's are observed, the rate of infusion can be increased to complete administration of the drug over one hour. The patient should be dosed once every 4 weeks, for as long as the patient does not shows any evidence of cardiotoxicity and continues to tolerate treatment. A minimum of 4 courses is recommended because 4 months was the median time to response in clinical trial reports. Adverse events such as Palmar Plantar Erythema (PPE), stomatitis and hematologic toxicity may be managed by delay or reduction in dose. Pretreatment with or concomitant use of antiemetics may be considered.

In AIDS Kaposi syndrome patients, Doxorubicin HCl liposome injection should be administered intravenously with (Doxorubicin HCl equivalent) 20 mg/m2 over 30 minutes, once every three weeks as long as patients respond satisfactorily and tolerate treatment.

Limited clinical experience exists in treating hepatically impaired patients with i-dox®, however based on experience with Doxorubicin HCl, it is recommended that the dose of i-dox® should be reduced if bilirubin level is elevated. When serum bilirubin is between 1.2 - 3.0 mg/dL administer 1/2 of the normal dose, and when the level is > 3 mg/dL administer 1/4th of the normal dose.

Breast Cancer/Ovarian Cancer Patients

Doxorubicin HCl liposome injection is administered intravenously at a dose of 50 mg/m^2 body surface, once every 4 weeks for as long as the disease does not progress, and the patient shows no

evidence of clinical cardiotoxicity and continues to tolerate treatment.
For doses < 90 mg: dilute Doxorubicin HCl liposome injection in 250 mL (50 mg/mL) (5%) Dextrose USP solution for infusion.
For doses ≥90 mg: dilute Doxorubicin HCl liposome injection in 500 mL (50 mg/mL) (5%) Dextrose USP solution for infusion.

The use of any other diluent or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of Doxorubicin HCl liposome injection.

To minimize the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent Doxorubicin HCl liposome injection infusions may be administered over a 60-minute period.

Patients With Multiple Myeloma
In multiple myeloma patients Bortezomib is administered at a dose of 1.3 mg/m^2 as intravenous bolus on days 1, 4, 8 and 11, every three weeks. On day 4 following bortezomib, Doxorubicin HCl liposome injection 30 mg/m2 should be administered as a 1-hr intravenous infusion. With the first on day 4 following bortezomib dose, an initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over one hour. Patients may be treated for up to 8 cycles until disease progression or the occurrence of unacceptable toxicity.

Dose Modification Guidelines have been proposed since Doxorubicin HCl liposome injection exhibits nonlinear pharmacokinetics at 50 mg/m^2. Dose adjustments may thus result in non-proportional greater change in plasma concentration and exposure to the drug.
Patients should be carefully monitored for toxicity. Adverse events such as Palmar Plantar Erythema (PPE), hematologic toxicities, and stomatitis may be managed by dose delays and adjustments. Subsequent to the first appearance of a Grade 2 or higher adverse event, dosing should be adjusted and or delayed as described in the following tables and should not be increased at any given time.

Palmar Planthar Erythrodyesthesia	
Toxicity Grade	**Dose adjustment**

1. Mild erythema, swelling or desquamation Not interfering with daily activities	Redose unless the patient has experienced previous grade 3 or 4 toxicity. If so delay upto 2 weeks and decrease dose by 25%. Return the original dose interval
2. Erythema, desquamation or swelling interfering with but not precluding normal physical activities small blisters or ulceration less than 2cm in diameter	Delay dosing upto 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution Doxorubicin should be discontinued.
3. Blistering, ulceration or swelling interfering with walking or normal daily activities regular Clothing cannot be worn.	Delay dosing upto 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose. If after 2 weeks there is no resolution Doxorubicin should be discontinued.
4. Diffuse or local process causing infectious Complications or a bed ridden state or hospitalization	Delay dosing upto 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose. If after 2 weeks there is no resolution Doxorubicin should be discontinued.

Haematological Toxicity			
Grade	**ANC**	**Platelets**	**Modifications**
1	1500-1900	75000-150000	Resume treatment with no dose reduction
2	1000-<1500	50000-<75000	Wait until ANC ≥1500 and platelets ≥ 75000; redose with no dose reduction
3	500-999	25000-<50000	Wait until ANC ≥1500 and platelets ≥ 75000; redose with no dose reduction
4	<500	<25000	Wait until ANC ≥1500 and platelets ≥ 75000; redose at 25% dose reduction or continue full dose with cytokine support

4.3 Contraindications

Hypersensitivity to the active substance doxorubicin hydrochloride or to any of the excipients.
Doxorubicin Hydrochloride is contra-indicated in patients with pre-existing myelosuppression (e.g. induced by previous antitumour treatment).
Dosage should not be repeated in the presence or development of bone marrow depression or buccal ulceration. The latter may be preceded by premonitory buccal burning sensations and repetition in the presence of this symptom is not advised.

Doxorubicin Hydrochloride is contraindicated in patients with impaired cardiac function and in patients who have been treated previously with complete cumulative doses of anthracyclines, Special warnings and precautions for use). In patients who have received anthracyclines previously, addition of further anthracycline therapy can be contemplated only after careful assessment of the cardiac status of the patient. The potential benefit of additional anthracycline therapy must carefully be weighed against the possible risks of cardiotoxicity.
Doxorubicin Hydrochloride is further contraindicated in patients with increased haemorrhagic tendency, stomatitis, generalised infections, markedly impaired liver function and cystitis (in the case of intravesical application).

4.4 Special warnings and precautions for use

Hypersensitivity to the active substance doxorubicin hydrochloride or to any of the excipients.
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Dosage should not be repeated in the presence or development

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4.5 *Interaction with other medicinal products and other forms of interaction*

Concurrent administration of other antineoplastic agents, e.g.: anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, dactinomycin, fluorouracil, mitomycin C and taxanes can potentiate the risk of doxorubicin-induced congestive heart failure. The disposition of doxorubicin was found to be significantly altered when it was administered immediately after a short intravenous infusion of paclitaxel. The co-administration of paclitaxel causes a decreased clearance of doxorubicin and more neutropenic and stomatitis episodes have been observed.

Increased cardiotoxicity has also been reported after simultaneous intake of cardioactive drugs, e.g., calcium channel blockers and verapamil (with an increase of doxorubicin peak levels, terminal-half life and volume of distribution). The bioavailibility of digoxin decreases during doxorubicin therapy. Careful monitoring of the heart function is required in all such concomitant therapeutic regimens. Inhibitors of cytochrome P-450 (e.g. cimetidine) may decrease the metabolism of doxorubicin, with a possible increase in toxic effects, especially in cardiotoxicity. Drugs inducing cytochrome P-450 (e.g. rifampicin, barbiturates including phenobarbital) may increase the metabolism of doxorubicin, possibly decreasing the efficacy of doxorubicin. If doxorubicin therapy is followed by administration of cyclophosphamide, an increased rate of haemorrhagic cystitis has been reported.
The absorption of antiepileptic drugs (e.g. carbamazepine, phenytoin, valproate) is decreased after concomitant use of doxorubicin.

As doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. mercaptopurine, methotrexate, streptozocin) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the drug. Dosing of doxorubicin must be modified if concomitant therapy with hepatotoxic drugs is mandatory.
Co-administration of heparin and doxorubicin can lead to an increase in the rate of doxorubicin clearance. Furthermore, precipitates may form and lead to a loss of efficacy of both drugs.
Disturbed haemotopoesis has been observed after co-administration of substances influencing the bonemarrow function (e.g. amidopyrine derivatives, antiretroviral drugs, chloramphenicol, phenytoin, sulphonamides). Increased neutropenia and thrombocytopenia have been reported after simultaneous use of progesterone. Marked nephrotoxicity of Amphotericin B can occur during doxorubicin therapy.
Live vaccines must not be used during doxorubicin therapy due to the risk of generalised disease, which may be lethal. The risk is increased in patients who are immunodepressed due to the underlying disease.

4.6 Pregnancy and lactation

Pregnancy

Doxorubicin has been found in foetal tissue (liver, kidney, lungs) at
concentrations several times those in maternal plasma indicating that it does pass the placenta. Doxorubicin proved to be highly teratogenic in rats and mutagenic in the Ames test. Pregnancy is therefore a contraindication for Doxorubicin Hydrochloride.
For safety reasons, men wanting a baby should preserve unexposed sperm prior to treatment with Doxorubicin and abstain from engendering a child during and 6 months after therapy. Women with childbearing potential should avoid pregnancy during doxorubicin therapy and 6 months thereafter.

Lactation

The drug has been shown to concentrate in human milk. Because of the potential for serious adverse reactions in nursing infants a decision should be made whether to discontinue breast-feeding or the drug, taking into account the importance of the drug for the woman.

4.7 Effects on ability to drive and use machines

Drowsiness may occur.

4.8 Undesirable effects

General

Bone Marrow Depression (myelosuppression):

There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematological monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10 – 14 days after treatment, with recovery usually occurring by the 21st day. White blood cell counts as low as $1000/mm^3$ is to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored, since they may also be depressed.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone infiltration by tumour, impaired liver function (when appropriate dosage reduction has not been adopted) and simultaneous treatment with other myelosuppressive agents. Haematological toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or haemorrhage.

Immunosuppression: Doxorubicin is a powerful but temporary immunosuppressant agent. Appropriate measures should be taken to prevent secondary infection.

Enhanced toxicity: It has been reported that doxorubicin may enhance the severity of the toxicity of other anticancer therapies, such as cyclophosphamide induced haemorrhagic cystitis, mucositis induced by radiotherapy, hepatotoxicity of 6-mercaptopurine and the toxicity of streptozocin or methotrexate.

Infertility: Doxorubicin may cause infertility during the time of drug administration. Although ovulation and menstruation appear to return after termination of therapy, there is only scarce information about the restoration of male fertility.

Hepatic impairment: Toxicity to recommended doses of doxorubicin is enhanced by hepatic impairment. It is recommended that an evaluation of hepatic function be carried out prior to individual dosing, using conventional clinical laboratory tests such as AST, ALT, alkaline phosphatase, bilirubin and BSP. If required, dosage schedules should be reduced accordingly.

The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA damaging antineoplastic agents. Such cases could have a short (1 - 3 year) latency period.

Adverse reactions

More frequent reactions

Cardiovascular: Cardiotoxicity, i.e., cardiomyopathy,

congestive heart failure, supraventricular tachycardia. Routine ECG monitoring is recommended and caution should be exercised in patients with impaired cardiac function. Severe cardiac failure may occur suddenly, without premonitory ECG changes.

Vascular system: Phlebosclerosis.

Dermatological: Extravasation, skin necrosis, cellulitis, vesication, phlebitis, erythematous streaking along the vein proximal to the site of injection. Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally returns after treatment is stopped.

The risk of thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended above.

Gastrointestinal: Nausea and vomiting, mucositis (stomatitis and oesophagitis), diarrhoea, anorexia, ulceration and necrosis of the colon. Mucositis is a frequent and painful complication of doxorubicin treatment. It most commonly develops 5 to 10 days after treatment, and typically begins as a burning sensation in the mouth and pharynx. It may involve the vagina, rectum and oesophagus, and progress to ulceration with risk of secondary infection and usually subsides in 10 days. Retrospective comparison of the incidence of mucositis suggests that it is less frequent as the intervals between doses increase.

Mucositis may be severe in patients who have had previous irradiation to the mucosae.

General: Dehydration, facial flushing (if an injection has been given too rapidly). Doxorubicin may impart a red colour to the urine particularly to the first specimen passed after the injection, and patients should be advised that there is no cause for alarm.

Less frequent reactions

Dermatological: Urticarial rash, onycholysis, hyperpigmentation of nail beds and dermal increases (primarily in children in a few cases), recall of skin reaction due to prior radiotherapy.

Allergy: Fever, chills, urticaria, anaphylaxis.

Nervous System: Drowsiness.

Ocular: Conjunctivitis,

lacrimation. *Renal:* Renal

damage.

4.9 Overdose

The symptoms of overdosage are likely to be an extension of doxorubicin's pharmacological action.

Single doses of 250 mg and 500 mg of doxorubicin have proven to be fatal. Such doses may cause acute myocardial degeneration within 24 hours, and severe myelosuppression, the greatest effects of which are seen between 10 and 15 days after administration. Delayed cardiac failure may occur up to six months after the overdose. Treatment should aim to support the

patient during this period. Particular attention should be given to prevention and treatment of possible severe haemorrhage or infections secondary to severe, persistent bone marrow depression.

Blood transfusion and reverse barrier nursing may be considered. Hemoperfusion immediately after the overdose proved to be a rescue measure, too.
Delayed cardiac failure may occur up to six month after the overdose. Patients should be observed carefully and, should signs of cardiac failure arise, be treated along conventional lines.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances)
ATC code: L01DB01

Doxorubicin is an anthracycline antibiotic. It exerts its antineoplastic effect via cytotoxic mechanisms of action, especially intercalation into DNA, inhibition of the enzyme topoisomerase II, and formation of reactive oxygen species (ROS). All of these have a deleterious effect on DNA synthesis: Intercalation of the doxorubicin molecule leads to an inhibition of RNA and DNA polymerases by way of disturbances in base recognition and sequence specificity. The inhibition of topoisomerase II produces single and double strand breaks of the DNA helix. Scission of DNA also originates from the chemical reaction with highly reactive oxygen species like the hydroxyl radical OH. Mutagenesis and chromosomal aberrations are the consequences. The specificity of doxorubicin toxicity appears to be related primarily to proliferative activity of normal tissue. Thus, bone marrow, gastro-intestinal tract and gonads are the main normal tissues damaged.
An important cause of treatment failure with doxorubicin and other anthracyclines is the development of resistance. In an attempt to overcome cellular resistance to doxorubicin, the use of calcium antagonists such as verapamil has been considered since the primary target is the cell membrane. Verapamil inhibits the slow channel of calcium transport and can enhance cellular uptake of doxorubicin. A combination of doxorubicin and verapamil is associated with severe toxic effects in animal experiments.

5.2 Pharmacokinetic properties

Following intravenous injection, doxorubicin is rapidly cleared

from the blood, and distributed into tissues including lungs, liver, heart, spleen, lymph nodes, bone marrow and kidneys. Relatively low but persistent levels are found in tumour tissue. Doxorubicin undergoes rapid metabolism in the liver. Doxorubicinol is the most common metabolite, although a substantial fraction of patients forms doxorubicin-7-deoxyaglycone and doxorubicinol-7-deoxyaglycone. About 40 to 50% of a dose is excreted in bile within 7 days, of which about half is as unchanged drug. Only about 5 % of a dose is excreted in urine within 5 days. Doxorubicinol, the major (active) metabolite, is excreted in both bile and urine. It does not cross the blood-brain barrier, but does cross the placenta and is distributed into breast milk. The elimination of doxorubicin from the blood is triphasic with mean half-lives of 12 minutes, 3.3 hours and about 30 hours.

The volume of distribution V_d is 25 l; the degree of protein binding is 60–70%. There is substantial interpatient variation in biotransformation. Clearance is apparently not dose-related, but it is higher in men than in women.
Impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Dose reduction is generally advised although there is no clear relationship between liver function tests, doxorubicin clearance and clinical toxicity. Since doxorubicin and metabolites are excreted in the urine only to a minor degree, there are no clear indications that the pharmacokinetics or toxicity of doxorubicin are altered in patients with impaired renal function.

5.3 Preclinical safety data

Doxorubicin behaves as a typical inhibitor of cellular reproduction. Cytotoxicity to the most actively proliferating tissues is more prevalent and occurs earlier with respect to parenchymal damage.

Single dose toxicity

Intravenous LD_{50} values in different animal species have been reported as follows:
Mouse 9 – 21 mg/kg, rat 8 – 14 mg/kg, rabbit 6 mg/kg and dog 2.5 mg/kg. A clear dose-dependent acute toxicity was observed.

Repeated dose toxicity

In clinical practice, the chronic toxicity of doxorubicin is rather similar to that of other comparable cytotoxic substances used in chemotherapy of malignant neoplasms. However, due to its cardiotoxic adverse effects doxorubicin notably warrants special precautions.
Intravenous doses of 0.125 to 0.5 mg/kg/d were given to rabbits and dogs for 3 months. The lowest dose caused neither mortality nor other signs of toxicity (except for a mild inhibition of spermatogenesis).

With the higher doses mortality, hemorrhagic enterocolitis, arrest or reduction of body growth, alopecia and melanosis, total depression of hemopoiesis with particular damage to the platelets, blood coagulation changes, hypoproteinemia, hyperazotemia, morphologic renal damage and depression of spermatogenesis was observed.

Tumorigenicity and mutagenicity

Single i.v. doses of doxorubicin induce mammary tumours in rats. It is also highly potent in producing malignant transformations and mutations in mammalian cell systems in vitro. In the Salmonella/microsome mutagenicity test system (Salmonella typhimurium + rat liver microsome S-9 fraction) doxorubicin proved to be a positive carcinogen. It is thus concluded that doxorubicin may have carcinogenic potential in man.

Doxorubicin proved to be mutagenic in the standard plate incorporation method of the Ames reversion test. Doxorubicin was also strongly mutagenic against the frameshift-sensitive strain TA98, especially when Cu^{++} ions were present. In the dominant lethal heritable translocation and morphological specific locus test doxorubicin did not induce dominant lethal mutations in murine male germ cells but did induce dominant lethal mutations in female oocytes.

In the cytokinesis-block micronucleus assay, it demonstrated a significant increase in the rate of micronucleated cells and of chromosomal aberrations.

Toxicity to reproduction

With respect to fertility, embryonal and foetal toxicity clinical data in man are incomplete. A termination of pregnancy may not always be mandatory and can only be judged in individual cases. In any case, cardiologic and blood tests in the foetus or newborn child is strongly recommended. The risk of malformations and malfunctions in children is considered to be high. Doxorubicin has been found in foetal tissue (liver, kidney, lungs) at concentrations several times those in maternal plasma indicating that it passes the placenta. Doxorubicin proved to be highly teratogenic in rats and mutagenic in the Ames test. Pregnancy is therefore a contraindication for Doxorubicin Hydrochloride.

In animal experiments, toxic effects of doxorubicin on reproduction were observed. In the rat, doxorubicin is teratogenic after i.p. doses as low as 1.25 mg/kg/day. Characteristic malformations included oesophageal and intestinal atresia, tracheoesophageal fistula, hypoplasia of the urinary bladder and various cardiovascular anomalies. The frequency of anomalies rose sharply as the dose increased.

At 2.25 mg/kg/day, all embryos were abnormal, and doxorubicin at 2.5 mg/kg/day led to resorption of all embryos. Teratogenicity

in late organogenesis (reduction anomalies of the distal limbs) was also demonstrated in rat embryo cultures in the concentration range of 0.1 – 20
_Mol/l.
In another experiment with female Sprague-Dawley rats, treated i.p. 1 - 10 mg/kg doxorubicin, the examination of the embryos revealed specific teratogenic effects on the caudal region. Histological examination showed signs of cell death at the level of the gut epithelium and bronchial bar mesenchyme. In the latter experiment, the highest dose of doxorubicin was maternolethal. The fetuses showed a dose-related increase of specific malformations of the digestive system (oesophageal and intestinal atresia, stomach hypoplasia,), urinary system (bladder agenesis or hypoplasia, hydronephrosis), and cardiovascular malformations.
The doxorubicin-treated foetal rat is an excellent model for studying the so-called VATER association (vertebral defects, anorectal anomaly, tracheoesophageal fistula with oesophageal atresia, and Radial dysplasia). Exposure of the rat foetus produces a spectrum of anomalies, including oesophageal atresia and other features of VATER association. Vertebral and rib anomalies e.g. were found in 54 % and limb anomalies in 35% of foetuses exposed to teratogenic doses of doxorubicin in utero.
In rats decreased weights of genital organs, an extremely decreased sperm count, a low sperm motility, a low implantation rate, a decreased number of spermatogonia and a decreased number of live fetuses were observed after 4 weeks of treatment with doses of 1 or 2 mg/kg. After 9 weeks of treatment, genital organs showed atrophy.
Doxorubicin was not teratogenic in the rabbit when given at IV doses up to
0.6 mg/kg/day, but a high incidence of abortion occurred.

In the chicken, doxorubicin is toxic and teratogenic during the period of early organogenesis of the chick embryos after eggs received a single injection on days 1 and 2 of incubation. Doxorubicin caused embryonic death, stunted growth, and various gross morphological malformations. LD50 values were 2.5 g/egg on day 1 and 0.9 g/egg on day 2.

Neurotoxicity
In ganglion cells of the peripheral nervous system and in spinal, paravertebral and trigeminal ganglia, loss of neurones was observed in rats after IV injections of 10 mg/kg. The animals developed severe posterior limb ataxia and mild ataxia of the forelimbs.

6. *Pharmaceutical particulars*

6.1 List of excipients

Hydrogenated Soy Phosphatidyl Choline, N-(Carbonyl

methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (Mper-dspe), Cholesterol USNF, ethyl alcohol USP, Ammonium Sulphate USNF, Water for Injection USP, Sucrose USNF, Doxorubicin Hydrochloride USP, L-Histidine USP, 1M Hydrochloric acid USP, Sodium Hydroxide USNF, Sucrose USP

6.2 Incompatibilities

Doxorubicin should not be mixed with heparin as a precipitate may form and it should not be mixed with 5-fluorouracil as degradation may occur. Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.

6.3 ***Shelf life:*** 2 Years

6.4 Special precautions for storage

Refrigerate unopened vials of i-dox® between 2-8 °C (36-46 °F) but avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on i-dox®.

6.5 Nature and contents of container:

I-dox® (Doxorubicin Hydrochloride Pegylated Liposomal Injection) is supplied as a sterile, translucent, red liposomal dispersion in 10 ml single use glass vial; each vial contains 20 mg of Doxorubicin HCl respectively at a concentration of 2 mg/ml. Refrigerate between 2-8 °C. Avoid freezing.

6.6 Special precautions for disposal

Caution should be exercised in the handling and preparation of i-dox®, the use of gloves is mandatory. If i-dox® comes into contact with skin or mucosa, wash thoroughly with soap and water. i-dox® should be considered as an irritant and precautions should be taken to avoid extravasation which may occur with or without an accompanying stinging or burning sensation. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. i-dox® must not be given by the intramuscular or subcutaneous route. i-dox® should be handled and disposed of in a manner consistent with other anticancer drugs

7. Manufacturer

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