1.3.1	Summary of product characteristics

1 Summary of Product Characteristic (Product Data Sheet)

1.1 Name of the Medicinal Product

(a) Product Name : Doxorubicin Hydrochloride for Injection BP 50mg/Vial

(b) Strength : 50mg/Vial

(c) Pharmaceutical Dosage Form : Dry injection

1.2 Quality and Quantitative Composition

(a) Qualitative Declaration, the active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant.

Each Lyophilized vial contains:

Doxorubicin Hydrochloride BP……50 mg.

(b) Quantitative Declaration, the quantity of the active substance must be expressed per dosage unit

Sr. NO.	Name of Ingredients	Function of ingredients	Quantity (per ml)	Quantity required per ml	Overage (%)	Qty. required per ml	Water /LOD content (%)	Total Qty. required per ml
Active								
1.	Doxorubicin Hydrochloride BP	Active Ingredient	50.0 mg.	50.0 mg.	Nil	50.0 mg.	Nil	50.0 mg.

1.3Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g: Red colored Lyophilized powder filled in Clear type-I glass vial with paper label and sealed with green colored flip off. Each 30ml clear glass vial packed in a printed carton with leaflet.

1.4 Clinical Particulars

(a) Therapeutic indications:

Antimitotic and cytotoxic. Doxorubicin has been used successfully 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 breast and lung carcinomas.

Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs. Doxorubicin cannot be used as an antibacterial agent.

(b) Posology and method of administration:

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

The solution is given via the tubing of a freely running intravenous infusion, taking not less than 3 minutes and not more than 10 minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis, vesication and necrosis. 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).

Dosage is usually calculated on the basis of body surface area. As a single agent, the recommended standard starting dose of doxorubicin per cycle in adults is 60-75mg/m^2 of body surface area. The total starting dose per cycle may be given as a single dose or divided over 3 successive days or in divided doses given on days 1 and 8. Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), each treatment cycle can be repeated every 3 to 4 weeks. If it is used in combination with other antitumour agents having overlapping toxicity, the dosage of doxorubicin may need to be reduced to 30-60mg/m^2 every three weeks.

If dosage is calculated on the basis of body weight, it has been shown that giving doxorubicin as a single dose every three weeks greatly reduces the distressing toxic effect, mucositis. However, there are still some who believe that dividing the dose over three successive days (0.4-0.8mg/kg or 20-25mg/m^2 on each day) gives greater effectiveness though at the cost of higher toxicity. If dosage is to be calculated on the basis of body weight, 1.2-2.4 mg/kg should be given as a single dose every three weeks.

Administration of doxorubicin in a weekly regimen has been shown to be as effective as the 3-weekly regimen. The recommended dosage is 20mg/m^2 weekly, although, objective responses have been seen at 16mg/m^2. Weekly administration leads to a reduction in cardiotoxicity.

Dosage may also need to be reduced in children, obese patients and the elderly.

Lower starting doses or longer intervals between cycles may need to be considered for heavily pre-treated patients, or patients with neoplastic bone marrow infiltration (see section 4.4).

Hepatic dysfunction

If hepatic function is impaired, doxorubicin dosage should be reduced according to the following table:

Serum Bilirubin Levels	**Recommended Dose**
1.2 – 3.0 mg/100ml	50% Normal dose
> 3.0 mg/100ml	25% Normal dose

Doxorubicin should not be administered to patients with severe hepatic impairment

(c) Contraindications:

Hypersensitivity to doxorubicin or to any of the excipients listed in section 6.1, 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

(d) Special warning and precautions for use:

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

Patients should recover from the 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).

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 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, 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 dyspnoea, pulmonary oedema, dependent oedema, 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.

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). 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 approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

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.

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.

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

Haematologic Toxicity

Doxorubicin may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia 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 anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Secondary Leukaemia

Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs or when doses of the anthracyclines have been escalated. These leukaemias can have a 1 to 3 year latency period.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Doxorubicin was genotoxic and mutagenic *in vitro* and *in vivo* tests.

In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhoea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

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.

Liver 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 the drug with an increase in overall toxicity. Lower doses are recommended in these patients (see section 4.2). Patients with severe hepatic impairment should not receive doxorubicin (see section 4.3).

Other

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced haemorrhagic 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.

Tumour-Lysis Syndrome

Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumour-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 hyperuricaemia may minimize potential complications of tumour lysis syndrome.

Vaccinations

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.

(e) Interaction with other medicinal products and other forms of interactions:

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.

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 haematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of cyclosporine and doxorubicin.

High dose cyclosporine increases the serum levels and myelotoxicity of doxorubicin.

Doxorubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastrointestinal effects (see section 4.4). 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), require 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 a smaller increase is observed when doxorubicin is administered prior to paclitaxel.

In a clinical study, an increase in doxorubicin AUC of 21% was observed when given with sorafenib 400 mg twice daily. The clinical significance of this finding is unknown.

(f) Pregnancy and lactation:

Pregnancy

Doxorubicin has harmful pharmacological effects on pregnancy and/or the foetus/newborn child.

Due to the embryotoxic potential of doxorubicin, this drug should not be used during pregnancy unless clearly necessary. If a woman receives doxorubicin during pregnancy or becomes pregnant whilst taking the drug, she should be warned of the potential hazard to the foetus. Women of childbearing potential have to use effective contraception during treatment (see section 4.4).

Breast-feeding

Doxorubicin is secreted into breast milk. Women should not breastfeed while undergoing treatment with doxorubicin.

(g) Effects on ability to drive and use machine:

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

(h) 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).

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, 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]

[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)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

(i) Overdose:

Single doses of 250mg and 500mg of doxorubicin have proved fatal. Such doses may cause acute myocardial degeneration within 24 hours and severe myelosupression (mainly leucopenia and thromobocytopenia), the effects of which are greatest between 10 and 15 days after

administration. Treatment should aim to support the patient during this period and should utilise such measures as blood transfusions and reverse barrier nursing.

Acute overdose with doxorubicin will result in gastrointestinal toxic effects (mainly mucositis). This generally appears early after drug administration, but most patients recover from this within three weeks.

Delayed cardiac failure may occur up to six months after the overdosage. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines.

1.5 Pharmacological Properties

Pharmacodynamic Properties:

Pharmacotherapeutic group: Anthracyclines and related substances, ATC code: L01DB01

Doxorubicin is an antitumour agent. Tumour cells are probably killed through drug-induced alterations of nucleic acid synthesis although the exact mechanism of action has not yet been clearly elucidated.

Proposed mechanism of action include:

DNA intercalation (leading to an inhibition of synthesis of DNA, RNA and proteins), formation of highly reactive free-radicals and superoxides, chelation of divalent cations, the inhibition of Na-K ATPase and the binding of doxorubicin to certain constituents of cell membranes (particularly to the membrane lipids, spectrin and cardiolipin). Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bone-marrow. Doxorubicin does not cross the blood-brain barrier.

(b) Pharmacokinetic Properties:

After IV administration, the plasma disappearance curve of doxorubicin is triphasic with half-lives of 12 minutes, 3.3 hours and 30 hours. The relatively long terminal elimination half-life reflects doxorubicin's distribution into a deep tissue compartment. Only about 33 to 50% of fluorescent or tritiated drug (or degradation products), respectively, can be accounted for in urine, bile and faeces for up to 5 days after IV administration. The remainder of the doxorubicin and degradation products appear to be retained for long periods of time in body tissues.

In cancer patients, doxorubicin is reduced to adriamycinol, which is an active cytotoxic agent. This reduction appears to be catalysed by cytoplasmic and pH-dependent aldo-keto reductases that are found in all tissues and play an important role in determining the overall pharmacokinetics of doxorubicin.

Microsomal glycosidases present in most tissues split doxorubicin and adriamycinol into inactive aglycones. The aglycones may then undergo 0-demethylation, followed by conjugation to sulphate or glucuronide esters, and excretion in the bile.

(c) Preclinical Safety Data:

No information in addition to that presented elsewhere in this Summary of Product Characteristics is available.

1.6 Pharmaceutical Particulars

(a) List of excipients:

Lactose BP
Methyl paraben BP
Water for injection BP

(b) Incompatibilities:

None

(c) Shelf life: 36 Months

(d) Special precautions for storage: Store between temperature 20℃ to 25℃. Protect from light. Keep out of the reach of children.

(e) Nature and contents of container: 30ml clear glass vial packed in a printed carton with leaflet.

1.7 Marketing Authorization Holder

Name :

Address :

Phone :

Fax :

E-mail:

1.8 Marketing Authorization Numbers