SUMMARY OF PRODUCT CHARACTERISTIC

1 NAME OF THE MEDICINAL PRODUCT

DOXUTEC 50 (Doxorubicin Hydrochloride Injection USP 50 mg/25ml)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains

Doxorubicin Hydrochloride USP 2.0 mg

Sodium Chloride USP 9.0 mg

Sodium Acetone Bisulfite IH 2.0 mg

Citric Acid USP To adjust pH

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 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.

4.2 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 minimizes 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. 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 agent shaving 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 or20-25mg/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.

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.

4.3Contraindications

Hypersensitivity to doxorubicin or to any of the excipients or 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

4.4 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.

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.

4.5 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.

Lactation

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

4.6 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 Overdose

Single doses of 250 mg and 500 mg 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic, **ATC code:** L01DB01

Mechanism of action

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.

5.2 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.

5.3 Preclinical safety data

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

6. Pharmaceutical Particulars

6.1 List of excipients

- Sodium Chloride USP
- Sodium Acetone Bisulfite IH
- Citric Acid USP
- Water for Injection USP

6.2 Shelf life

24 Months

6.3 Special precautions for storage

Store in a refrigerator (2° to 8°). Do not freeze. Store protected from light.