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Summary of Product Characteristics last updated on the eMC: 18/01/2010

Doxorubicin Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

Doxorubicin Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxorubicin Hydrochloride 2mg/ml

3. PHARMACEUTICAL FORM

Solution for intravenous use.

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 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 Special Warnings and Precaution for Use).

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/m² 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/m² 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/m² 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/m² weekly, although, objective responses have been seen at 16mg/m². 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 Special Warnings and Precautions for Use).

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 (see section 4.3 Contra-indications).

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).

4.4 Special warnings 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 Posology and Method of Administration).

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/m² slowly increases up to the total cumulative dose of 450-550 mg/m². Thereafter, the risk of developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m².

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. 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 half-life of trastuzumab is approximately 28.5 days and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 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 Posology and Method of Administration). Patients with severe hepatic impairment should not receive doxorubicin (see section 4.3 Contraindications).

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.

Tumor-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

4.5 Interaction with other medicinal products and other forms of interaction

High dose cyclosporin 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 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), 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.

4.6 Pregnancy and lactation

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 Special Warnings and Precautions for Use).

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

4.7 Effects on ability to drive and use machines

None stated

4.8 Undesirable effects

The following adverse events (not listed in order of frequency) have been reported in association with doxorubicin therapy:

Neoplasms Benign and Malignant (including cysts and polyps):

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. Acute lymphocytic leukaemia and acute myelogenous leukaemia.

Blood and Lymphatic System Disorders:

Haematological monitoring should be undertaken regularly in both haematological and non haematological conditions, because of the possibility of bone-marrow depression which may become evident around ten days from the time of administration. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death. Leucopenia, neutropenia, anaemia and thrombocytopenia.

Immune System Disorders:

Anaphylaxis.

Metabolism and Nutrition Disorders:

Anorexia, dehydration and hyperuricaemia.

Eye Disorders:

Conjunctivitis / keratitis and lacrimation.

Cardiac Disorders:

Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. 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. Tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reduction in left ventricular ejection fraction and congestive heart failure.

Vascular Disorders:

Phlebitis, thrombophlebitis, thromboembolism, hot flushes and shock.

Gastrointestinal Disorders:

Nausea, vomiting and mucositis/stomatitis, hyperpigmentation of oral mucosa, oesophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, diarrhoea and colitis.

Hepatobiliary Disorders:

Changes in transaminase levels.

Skin and Subcutaneous Tissue Disorders:

Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally resumes after treatment is stopped. Skin rashes/itch, local toxicity, skin changes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin ('radiation recall reaction'), urticaria, acral erythema and plantar-palmar dysaesthesia.

Renal and Urological Disorders:

Doxorubicin may impart a red colour to urine particularly to the first specimen passed after the injection and patients should be advised that this is no cause for alarm.

Reproductive System and Breast Disorders:

Amenorrhoea, oligospermia and azospermia.

General Disorders and Administration Site Conditions:

The risk of thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended above. A stinging or burning sensation at the site of administration signifies a small degree of extravasation and the infusion should be stopped and re-started in another vein. Fever, malaise, asthenia and chills.

Investigations:

ECG abnormalities.

4.9 Overdose

Single doses of 250mg and 500mg of doxorubicin have proved fatal. Such doses may cause acute myocardial degeneration within 24 hours and severe myelosuppression (mainly leucopenia and thrombocytopenia), 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

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 have 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.

5.2 Pharmacokinetic properties

After i.v. 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 i.v. 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 nadph-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 O-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

Water for Injections Ph Eur

Sodium chloride Ph Eur

Hydrochloric acid Ph Eur

6.2 Incompatibilities

Doxorubicin should not be mixed with heparin as a precipitate may form and it is not recommended that doxorubicin be mixed with other drugs. 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

Store refrigerated between 2- 8°C

6.5 Nature and contents of container

Single glass vials of 5ml (10mg), 10ml (20mg), 25ml (50mg) and 100ml (200mg).

Single Cytosafe™ polypropylene vials of 5ml (10mg), 10ml (20mg), 25ml (50mg) and 100ml (200mg).

6.6 Special precautions for disposal and other handling

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, 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 and absorbent

paper.

- All items 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 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 graze the skin by using a scrubbing brush.
- In case of contact with eye(s), hold back the eyelid(s) and flush the affected eyes with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

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United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 03433/0127

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Renewed 22 June 2009

10. DATE OF REVISION OF THE TEXT

5th January 2010

Legal Category

POM

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