PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

DOXORUBICIN 10 mg/5 mL FRESENIUS concentrate for solution for infusion

DOXORUBICIN 50 mg/25 mL FRESENIUS concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

1 mL contains 2 mg doxorubicin hydrochloride.

Each 5 mL vial contains 10 mg doxorubicin hydrochloride.

Each 25 mL vial contains 50 mg doxorubicin hydrochloride.

Excipient with known effect:

Contains sodium 3,5 mg/mL (0,15 mmol)

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

The product is a clear, red solution, with pH 2,5 - 4,5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DOXORUBICIN FRESENIUS is indicated in:

- Acute leukaemias (Acute Lymphoblastic Leukaemia – ALL and Acute Myelogenous Leukaemia – AML), lymphomas and a number of solid tumours.
- Metastatic adenocarcinoma of the breast, carcinoma of the bladder, bronchogenic carcinoma and neuroblastoma.
- Metastatic thyroid carcinoma. Carcinoma of the endometrium, testes, prostate, cervix, head and neck and plasma-cell myeloma.
- It is active against carcinoma of the ovary when administered with cisplatin and cyclophosphamide.
- Concurrently with other cytotoxic medicines when administered for carcinoma of the breast and small (oat)-cell carcinoma of the lung.
- Wide range of sarcomas, including osteogenic, Ewing's and soft-tissue sarcoma.
- In the ABVD (doxorubicin / bleomycin / vinblastine / dacarbazine) combination it is effective in Hodgkin's disease.
- Concurrently in the BACOP combination in non-Hodgkin's lymphoma.

4.2 Posology and method of administration

Posology

Treatment of solid tumours:

When doxorubicin is administered as monotherapy, the recommended dose per cycle is 60 - 90 mg/m^2 of body surface area every 3 - 4 weeks.

Administration of doxorubicin in a weekly regimen of 10 - 20 mg/m^2 has also been shown to be effective. The medicine is generally given as a single dose per cycle; however, it is possible to give the medicine dosage per cycle in divided administrations:

- 0,6 mg/kg/day for 3 days (25 mg/m^2 for 3 days) OR
- 0,8 mg/kg/day for 2 days (30 mg/m^2 for 2 days) OR
- 1,6 mg/kg/day for 1 day (60 mg/m^2 for 1 day).

If DOXORUBICIN FRESENIUS is used in combination with other antitumour medicines, the recommended dose per cycle is in the 30 - 60 mg/m^2 range, repeated every 21 days.

As doxorubicin is a myelosuppressive substance, the interval between cycles may need to be increased, or the dosage reduced in patients whose white blood cell (WBC) counts (particularly neutrophils) are below the range of normal values before any treatment cycle.

Treatment of acute leukaemias:

In acute leukaemia the dosage schedule is based on the patient's response.

The recommended starting dose is 0,4 - 0,5 mg/kg/day for 3 days. According to the anti-leukaemia and myelosuppressive effect obtained, this course can be repeated a

second or even a third time with an interval between courses of not less than 7 - 10 days.

Special populations

Dosage may also need to be reduced in children, in the elderly, obese patients and in pre-treated patients in whom the marrow reserve may be low.

Hepatic dysfunction:

In the presence of impaired hepatic function, it is suggested that doxorubicin dosage be reduced as follows:

Serum bilirubin	**Dose reduction**
1,2 - 3 mg/100 mL	50 % (i.e. 50 % of normal dose to be given)
> 3 mg/100 mL	75 % (i.e. 25 % of normal dose to be given)

DOXORUBICIN FRESENIUS should not be administered to patients with severe hepatic impairment (see section 4.3).

Method of administration

Precaution to be taken before manipulating or administering the product.

See section 6.6 for instructions for preparation and handling.

DOXORUBICIN FRESENIUS is administered by intravenous injection. DOXORUBICIN FRESENIUS should **not** be given orally, intramuscularly or subcutaneously.

Intravenous administration:

Intravenous administration of DOXORUBICIN FRESENIUS should be performed with caution (see section 6.6). It is recommended that the diluted solution of DOXORUBICIN

FRESENIUS be administered into the tubing of a freely flowing intravenous infusion (isotonic sodium chloride or 5 % glucose solution) over a period of 3 to 5 minutes. This technique is intended to minimise the risk of thrombosis or perivenous extravasation.

4.3 Contraindications

- Hypersensitivity to doxorubicin or any other component of DOXORUBICIN FRESENIUS (listed in section 6.1).
- Hypersensitivity to other anthracyclines or anthracenediones.
- Persistent myelosuppression
- Hepatic impairment
- Myocardial insufficiency
- Recent myocardial infarction
- Severe dysrhythmias
- Previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (see section 4.4).
- Pregnancy and/or lactation (see section 4.6).

4.4 Special warnings and precautions for use

DOXORUBICIN FRESENIUS should be administered only under the supervision of a doctor experienced in cancer chemotherapy.

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

DOXORUBICIN FRESENIUS is incompatible with heparin and should also not be mixed with other medicines (see section 6.2).

DOXORUBICIN FRESENIUS should be given with great care, in reduced doses, to elderly patients and those with hepatic impairment.

The systemic clearance of DOXORUBICIN FRESENIUS is reduced in obese patients (i.e. > 130 % ideal body weight) (see section 4.2).

Control of the left ventricular function

Analysis of left ventricular ejection fraction (LVEF) using ultrasound or heart scintigraphy should be performed in order to optimise the heart condition of the patient. This control should be made prior to the start of the treatment and after each accumulated dose of approximately 100 mg/m^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. Tachydysrhythmias, 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 FRESENIUS treatment.

Flattening and widening of the QRS-complex beyond normal limits may indicate doxorubicin hydrochloride-induced cardiomyopathy. As a rule, in patients with a normal LVEF baseline value (= 50 %), a 10 % decrease of absolute value or dropping below the 50 % threshold indicates cardiac dysfunction and in such situation treatment with DOXORUBICIN FRESENIUS should be carefully considered.

Late (i.e. delayed) events:

Delayed cardiotoxicity usually develops late in the course of therapy with DOXORUBICIN FRESENIUS 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 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 medicine.

Cardiac function should be assessed before patients undergo treatment with DOXORUBICIN FRESENIUS and should be monitored throughout therapy to minimise 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 FRESENIUS 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.

If the patient has other potential risk factors of cardiotoxicity (history of cardiovascular disease, previous therapy with other anthracyclines or anthracenediones, prior or concomitant radiotherapy to the mediastinal/pericardial area, and concomitant use of medicines with the ability to suppress cardiac contractility, including cyclophosphamide and 5-fluoruracil), cardiotoxicity with DOXORUBICIN FRESENIUS may occur at lower cumulative doses and cardiac function should be carefully monitored.

Children and adolescents are at an increased risk for developing delayed cardiotoxicity following DOXORUBICIN FRESENIUS 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.

To reduce the effects of cardiotoxicity the total cumulative dose of doxorubicin should not exceed 500 mg/m^2 body surface area.

Haematologic toxicity

Blood counts and measurement of haemoglobin concentration should be carried out routinely.

DOXORUBICIN FRESENIUS may produce myelosuppression (see section 4.8).

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 DOXORUBICIN FRESENIUS. Leukopenia and neutropenia generally reach the nadir between days 10 and 14 after medicine 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 acute myeloid leukaemia with or without a preleukaemic phase, has been reported in patients concurrently treated with DOXORUBICIN FRESENIUS in combination with other DNA-damaging antineoplastic medicines. These leukaemias can have a 1 to 3 year latency period.

Fertility impairment

DOXORUBICIN FRESENIUS can have genotoxic effects. Doxorubicin may cause infertility during the time of medicine administration. In women, doxorubicin may cause amenorrhea. Although ovulation and menstruation appear to return after termination of therapy, premature menopause can occur. Women should not become pregnant during and up to 6 months after treatment.

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 measures. Also are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation (or cryo-preservation) of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with doxorubicin.

Gastrointestinal

Doxorubicin is emetogenic. Mucositis/stomatitis generally appears early after medicine 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.

An antiemetic prophylaxis is recommended.

DOXORUBICIN FRESENIUS should not be used in the presence of inflammation, ulceration or diarrhoea.

Liver function

Before starting the treatment, it is recommended to measure the liver function by using conventional tests such as AST, ALT, ALP and bilirubin as well as the renal function.

The major route of elimination of doxorubicin is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with DOXORUBICIN FRESENIUS. Patients with elevated bilirubin may experience slower clearance of medicine 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 FRESENIUS (see section 4.3).

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 minimise the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2 and 6.6).

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 FRESENIUS, the infusion should be stopped immediately; the needle should be left in place for a short time and then be removed after short aspiration.

If extravasation is suspected or occurs, the injection should be discontinued and restarted in a different blood vessel. Cooling the area for 24 hours can reduce the discomfort. The patient should be carefully monitored for several weeks. Surgical measures might be necessary.

Radiotherapy

Radiation-induced toxicities (myocardium, mucosa, skin and liver) have also been reported. Special caution is mandatory for patients who have had radiotherapy previously, are having radiotherapy concurrently or are planning to have radiotherapy. These patients are at special risk of local reactions in the radiation field (recall phenomenon) if DOXORUBICIN FRESENIUS is used. Severe, sometimes fatal, hepatotoxicity (liver damage) has been reported in this connection. Prior radiation to the mediastinum increases the cardiotoxicity of doxorubicin. The cumulative dose of 400 mg/m^2 must not be exceeded especially in this case.

Anticancer therapies:

DOXORUBICIN FRESENIUS may potentiate the toxicity of other anticancer therapies (see section 4.5). Exacerbation of cyclophosphamide-induced haemorrhagic cystitis

and enhanced hepatotoxicity of 6-mercaptopurine have been reported, as with other cytotoxic medicines, thrombophlebitis and thromboembolic phenomena including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of doxorubicin (see section 4.8).

Vaccines

DOXORUBICIN FRESENIUS is not recommended in combination with live, attenuated vaccines. Contact to persons recently vaccinated against polio should be avoided. Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicines including DOXORUBICIN FRESENIUS, may result in serious or fatal infections. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Tumour lysis syndrome:

DOXORUBICIN FRESENIUS may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies medicine-induced rapid lysis of neoplastic cells (tumour lysis syndrome) (see section 4.8). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumour lysis syndrome.

Other:

DOXORUBICIN FRESENIUS may impart a red colour to the urine. Patients should be cautioned that this does not pose any health hazards.

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 FRESENIUS contains 0,15 mmol (3,5 mg) sodium per mL. This should be taken into account by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

DOXORUBICIN FRESENIUS is mainly used in combination with other cytotoxic medicines. Additive toxicity may occur, especially bone marrow/haematologic and gastrointestinal effects (see section 4.4).

The use of DOXORUBICIN FRESENIUS in combination chemotherapy with other potentially cardiotoxic medicines, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment.

The use of trastuzumab in combination with anthracyclines (such as DOXORUBICIN FRESENIUS) is associated with a high cardiotoxic risk. Trastuzumab and anthracyclines should not be used in combination for the time being, except in well controlled clinical studies where the cardiac function is monitored. When anthracyclines are used after the end of a therapy with trastuzumab, an elevated risk of cardiotoxicity may result. The half-life of trastuzumab is approximately 28 - 38 days and may persist in the circulation for up to 27 weeks. If possible, there should be a sufficiently long interval (up to 27 weeks) between the end of a therapy with trastuzumab and the beginning of the anthracycline (DOXORUBICIN FRESENIUS) therapy. Careful monitoring of the cardiac function is imperative.

Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

DOXORUBICIN hepatotoxicity may be enhanced by other hepatotoxic treatment modalities (e.g. 6-mercaptopurine).

Doxorubicin undergoes metabolism via cytochrome P450 (CYP450) and is a substrate for the Pgp transporter. Concomitant administration of inhibitors of CYP450 and/or Pgp might lead to increased plasma concentrations of doxorubicin and thereby increased toxicity. Conversely, concomitant administration of inducers of CYP450, such as rifampicin and barbiturates, might decrease plasma concentrations of doxorubicin and reduce efficacy.

Concomitant administration of phenytoin may result in lower plasma phenytoin levels.

Paclitaxel administered shortly before doxorubicin may decrease clearance and increase plasma concentrations of doxorubicin. Some data indicate that this interaction is less pronounced when doxorubicin is administered before paclitaxel.

Ciclosporin, an inhibitor of CYP3A4 and Pgp, increased the AUC of doxorubicin and doxorubicinol by 55 % and 350 %, respectively. The combination might require dose adjustment. Cimetidine has also been shown to reduce the plasma clearance and increase the AUC of doxorubicin.

As doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic medicines (e.g. mercaptopurine, methotrexate, streptozocin) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the medicines. Dosing of DOXORUBICIN FRESENIUS must be modified if concomitant therapy with hepatotoxic medicines is mandatory.

Marked nephrotoxicity of amphotericin B can occur during DOXORUBICIN FRESENIUS therapy.

Elevated serum doxorubicin concentrations were reported after the concomitant administration of doxorubicin and ritonavir.

The toxic effects of DOXORUBICIN FRESENIUS therapy may be increased in a combination with other cytostatics (e.g. cytarabine, cisplatin, cyclophosphamide). Necroses of the large intestine with massive haemorrhage and severe infections in connection with combination therapies with cytarabine have been reported.

Clozapine may increase the risk and severity of the haematologic toxicity of DOXORUBICIN FRESENIUS.

Doxorubicin is a potent, radiosensitising substance (“radiosensitizer”), and recall phenomena induced by it may be life-threatening. Any preceding, concomitant or subsequent radiation therapy may increase the cardiotoxicity or hepatotoxicity of doxorubicin.

If DOXORUBICIN FRESENIUS therapy is followed by administration of cyclophosphamide, an increased rate of haemorrhagic cystitis has been reported.

DOXORUBICIN FRESENIUS therapy may lead to increased serum uric acid; therefore, dose adjustment of uric acid lowering medicines may be necessary.

DOXORUBICIN FRESENIUS may reduce oral bioavailability of digoxin.

During treatment with DOXORUBICIN FRESENIUS patients should not be actively vaccinated and should avoid contact with recently polio vaccinated persons (see section 4.4).

4.6 Fertility, pregnancy and lactation

The use of DOXORUBICIN FRESENIUS during pregnancy or lactation is contraindicated.

Women of childbearing potential

Women of childbearing age should avoid pregnancy during treatment and 7 months thereafter.

Women of childbearing potential must use effective contraception during DOXORUBICIN FRESENIUS therapy.

Pregnancy

DOXORUBICIN FRESENIUS crosses the placenta.

It can cause foetal harm when administered during pregnancy.

Breastfeeding

DOXORUBICIN FRESENIUS is distributed into breastmilk.

Mothers should discontinue breastfeeding prior to taking DOXORUBICIN FRESENIUS.

Fertility

For safety reasons, men wanting a baby should preserve unexposed sperm prior to treatment with doxorubicin and abstain from fathering a child during and 6 months after therapy (see section 4.4).

Male or female patients intending to have a child are advised to seek genetic counselling after treatment with DOXORUBICIN FRESENIUS.

4.7 Effect on ability to drive and use machines:

Due to the frequent occurrence of nausea and vomiting, driving cars and operation of machinery should be discouraged.

4.8 Undesirable effects

System organ class/ Frequency	Undesirable effect
Infections and infestations	
Frequent:	sepsis, septicaemia
Neoplasms benign and malignant	
Less frequent:	secondary acute myeloid leukaemia when in combination with antineoplastic medicines which damage the DNA. (see section 4.4), tumour lysis syndrome
Frequency unknown:	acute lymphocytic leukaemia and acute myelogenous leukaemia
Blood and lymphatic system disorders	
Frequent:	bone marrow depression, leukopenia and neutropenia
Less frequent:	anaemia, thrombocytopenia, bleeding, immunosuppressant effect
Immune system disorders	
Less frequent:	hypersensitivity reactions, anaphylactic reactions
Metabolism and nutrition disorders	
Frequent:	anorexia

Less frequent:	dehydration, uric acid nephropathy. This occurs most commonly during initial treatment of patients with leukaemia or lymphoma as a result of rapid cell breakdown that leads to elevated serum uric acid concentrations.
Nervous system disorders	
Less frequent:	headache
Eye disorders	
Less frequent:	conjunctivitis, lachrymation
Frequency unknown:	keratitis
Cardiac disorders	
Frequent:	cardiomyopathy (2 %: e.g. decrease of LVEF, dyspnoea)
Less frequent:	dysrhythmias, congestive heart failure
Frequency unknown:	asymptomatic reduction in LVEF and congestive heart failure. Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. (e.g. sinus tachycardia, tachydysrhythmia, ventricular tachycardia, bradycardia, atrioventricular and bundle-branch block). See section 4.4.
Vascular disorders	
Less frequent:	hypotension, phlebitis
Frequency unknown:	thrombophlebitis, thromboembolism, hot flushes, shock
Respiratory, thoracic and mediastinal disorders	
Frequency unknown:	bronchospasm, radiation pneumonitis

Gastrointestinal disorders

Frequent:	nausea, vomiting, mucositis/stomatitis, diarrhoea
Less frequent:	oesophagitis, abdominal pain, intestinal ulceration and perforation, buccal ulceration
Frequency unknown:	colitis, hyperpigmentation of oral mucosa

Hepato-biliary disorders

Frequency unknown:	hepatotoxicity, transient increase of liver enzymes

Skin and subcutaneous tissue disorders

Frequent:	alopecia, facial flushing
Less frequent:	itching, local hypersensitivity reaction of the field of radiation (recall phenomenon), urticaria, exanthema, local erythematous reactions along the vein which was used for the injection, hyperpigmentation of skin and nails, onycholysis
Frequency unknown:	tissue hypoxia, acral erythema and plantar-palmar dysaesthesia, photosensitivity

Renal and urinary disorders

Less frequent:	urine discolouration, hyperuricaemia, acute renal failure, nephrotoxicity, hyperphosphataemia
Frequency unknown:	acute renal failure

Reproductive system and breast disorders

Less frequent:	amenorrhoea, inhibition of spermatogenesis, gynaecomastia
Frequency unknown:	azoospermia (see section 4.4)

General disorders and administrative site conditions	
Less frequent:	fever, malaise, weakness, shivering, dizziness
Frequency unknown:	thrombophlebitis, streaking of the skin, stinging or burning sensation at the injection site (see section 4.4), asthenia
Investigations	
Frequency unknown:	ECG abnormalities
Surgical and medical procedures	
Frequency unknown:	extravasation can lead to severe cellulitis, vesication and local tissue necrosis (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Acute overdosage may cause gastrointestinal symptoms, buccal ulceration and bone marrow depression.

Should these symptoms occur therapy should be stopped.

A cumulative dosage above 500 mg/m^2 may cause irreversible cardiac failure. Treatment is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances

ATC code: L01DB01

Category A26 Cytostatic agents

Doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius* and displays broad activity against human neoplasms, including a variety of solid tumours.

The exact mechanism of the antitumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for most of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix, thus preventing their unwinding for replication. Other possible mechanisms of antineoplastic activity include binding to cell membrane lipids, thus altering a variety of cellular functions and interacting with topoisomerase II to form DNA-cleavable complexes.

5.2 Pharmacokinetic properties

Distribution:

Doxorubicin HCl is widely distributed into the extravascular compartments. It has a distribution half-life of 5 to 10 minutes and a steady state distribution volume in excess of 20 to 30 litres/kg. Doxorubicin does not cross the blood-brain barrier in detectable amounts but may cross the placenta and is distributed into breast milk. Binding of doxorubicin to plasma protein is extensive.

Metabolism:

Doxorubicin HCl undergoes rapid metabolism in the liver to various metabolites. The active metabolite is doxorubicinol (adriamycinol). It is eliminated by metabolic conversion to a variety of less active or inactive products.

Elimination:

The elimination half-life of doxorubicin and doxorubicinol is 20 to 48 hours. About 40 - 50 % of a dose is stated to be excreted in bile within 7 days, of which about half is unchanged. Only about 5 % of a dose is excreted in urine within 5 days. Clearance is delayed in the presence of hepatic dysfunction and at least a 50 % initial reduction in dose should be considered in patients with abnormal serum bilirubin levels. See section 4.2.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients are sodium chloride and water for injection.

6.2 Incompatibilities:

DO NOT MIX DOXORUBICIN FRESENIUS WITH OTHER MEDICINES, EXCEPT THOSE MENTIONED IN SECTION 6.6.

Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. DOXORUBICIN FRESENIUS should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

6.3 Shelf life

Shelf life of unopened vial

24 months.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

From a chemical and physical point of view, the product should be used immediately after first opening. Any unused portion must be discarded after use.

6.4 Special precautions for storage

Unopened vial:

Store in a refrigerator at 2° - 8 °C. Do not freeze. Keep vial in carton to protect from light.

Store in an upright position.

6.5 Nature and contents of the container

DOXORUBICIN 10 mg/5 mL FRESENIUS**:** 10 mg is packed in 5 mL clear colourless type I moulded glass vial with 5 mL fill, plugged with bromobutyl grey rubber stoppers with aluminium flip off seal.

Each vial may be shrink wrapped along with a plastic bottom and packaged in a mono-carton.

Not all pack sizes may be marketed.

DOXORUBICIN 50 mg/25 mL FRESENIUS**:** 50 mg is packed in 30 mL clear colourless type I, moulded glass vial with 25 mL fill, plugged with bromobutyl grey rubber stoppers with aluminium flip off seal.

Each vial may be shrink wrapped along with a plastic bottom and packaged in a mono-carton.

Not all pack sizes may be marketed.

6.6 Special precautions of disposal and other handling

DO NOT USE MATERIAL THAT SHOWS EVIDENCE OF PRECIPITATION OR ANY OTHER PARTICULATE MATTER**.**

DOXORUBICIN FRESENIUS is a potent cytotoxic medicine which should only be prescribed, prepared and administered by professionals who have been trained in the safe use of the preparation.

Preparation

This preparation is intended for single dose administration. The injection solution contains no preservative, and any unused portion of the vial should be discarded

immediately. DOXORUBICIN FRESENIUS is compatible with sodium chloride 0,9 % and dextrose 5 %.

1. Determine the dose of DOXORUBICIN FRESENIUS to be administered (based upon the recommended dose and the patient's body surface area).
2. Draw up the appropriate volume of DOXORUBICIN FRESENIUS up into a sterile syringe.
3. Aseptic technique must be strictly observed since no preservative or bacteriostatic substances are present in DOXORUBICIN FRESENIUS.
4. The appropriate dose of DOXORUBICIN FRESENIUS must be diluted in 0,9 % sodium chloride or dextrose 5 % in water for injection, prior to administration.
5. It is recommended that DOXORUBICIN FRESENIUS infusion line be connected through the side port of an intravenous infusion of 0,9 % sodium chloride or dextrose 5 % in water for injection.
6. The use of any diluents other than dextrose 5 % in water for infusion, or the presence of any bacteriostatic substance such as benzyl alcohol may cause precipitation of DOXORUBICIN FRESENIUS.

Do not use with in-line filters.

Guidelines for safe handling

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this medicine.
- 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.

7 HOLDER OF THE CERTIFICATES OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7 Growthpoint Park Business Park

162 Tonetti Street

Halfway House Extension 7

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South Africa

Telephone number: +27 (0)11 545 0000

8 REGISTRATION NUMBERS

DOXORUBICIN 10 mg/ 5 mL FRESENIUS: 48/26/0937

DOXORUBICIN 50 mg/25 mL FRESENIUS: 48/26/0938

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 June 2021

10. DATE OF REVISION OF THE TEXT

09 January 2025