COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Doxorubicine Accord 2 mg/ml concentrate for solution for infusion

(doxorubicin)

NL/H/4562/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Doxorubicine Accord 2 mg/ml concentrate for solution for infusion. The procedure was finalised in the United Kingdom (UK/H/1347/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Doxorubicin 2mg/ml Concentrate for Solution for Infusion

(doxorubicin hydrochloride)

UK/H/1347/001/DC

UK licence numbers: PL 20075/0109

Accord Healthcare Limited

LAY SUMMARY

On 11th March 2010, the MHRA granted Accord Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Doxorubicin 2mg/ml Concentrate for Solution for Infusion (PL 20075/0109, UK/H/1347/001/DC). This is a prescription-only medicine (POM) intended for use in adults only.

Doxorubicin is one of a group of medicines called anthracyclines. These drugs are also known as cancer drugs, chemotherapy, or "chemo". They are used in the treatment of various cancers to slow or stop the growth of cancer cells. A combination of different types of cancer drugs will often be used to achieve better results and minimize side effects.

Doxorubicin 2mg/ml Concentrate for Solution for Infusion is used to treat the following forms of cancer:

- breast cancer
- cancer of the connective tissue, ligaments, bone, muscle (sarcoma)
- cancer develops within the stomach or intestine
- lung cancer
- lymphomas, a cancer affecting the immune system
- leukaemia, a cancer that causes abnormal production of blood cell
- cancer of the thyroid gland
- advance ovarian and endometrial cancer (a cancer of the lining of the uterus or of the uterus)
- bladder cancer
- advance neuroblastoma (a cancer of the nerve cells commonly found in children)
- malignant renal tumour in children (Wilm´s tumour)
- myeloma (cancer of the bone marrow)

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Doxorubicin 2mg/ml Concentrate for Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information About Initial Procedure

Product Name	Doxorubicin 2mg/ml Concentrate for Solution for Infusion
Type of Application	Generic, Article 10.1
Active Substance	Doxorubicin hydrochloride
Form	Concentrate for solution for infusion
Strength	2mg / ml
MA Holder	Accord Healthcare Limited Sage House, 319, Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom
RMS	UK
CMS	AT, BE, BG, DE, DK, EE, ES, FI, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE and SI
Procedure Number	UK/H/1347/001/DC
Timetable	Day 210 (end of procedure) – 24th February 2010

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxorubicin 2 mg/ml Concentrate for Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 2 mg Doxorubicin hydrochloride

Each 5 ml vial contains 10 mg of Doxorubicin hydrochloride.
Each 25 ml vial contains 50 mg of Doxorubicin hydrochloride.
Each 100 ml vial contains 200 mg of Doxorubicin hydrochloride.
Excipient: Contains sodium 3.5 mg/ml (0.15 mmol)

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 a pH in the range of 2.5-3.5 and osmolality between 270 mOsm/kg to 320 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxorubicin is indicated in the following neoplastic conditions,
Examples include:

- Small-cell lung cancer (SCLC)
- Breast cancer
- Advanced ovarian carcinoma
- Intravesically for bladder cancer
- Neoadjuvant and adjuvant therapy of osteosarcoma
- Advanced soft-tissue sarcoma in adults
- Ewing's sarcoma
- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Acute lymphatic leukaemia
- Acute myeloblastic leukaemia
- Advanced multiple myeloma
- Advanced or recurrent endometrial carcinoma
- Wilms' tumour
- Advanced papillary/follicular thyroid cancer
- Anaplastic thyroid cancer
- Advanced neuroblastoma

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

4.2 Posology and method of administration

Doxorubicin Injection should be administered only under the supervision of a qualified physician with extensive experience in cytotoxic treatment. Also, patients must be carefully and frequently monitored during the treatment (see section 4.4)

Due to the risk of often lethal **cardiomyopathy**, the risks and benefits of the individual patient should be weighted before each application.

Doxorubicin is administered intravenously and intravesically and must not be administered orally, subcutaneously, intramuscularly or intrathecally. Doxorubicin can be administered intravenously as bolus within minutes, as short infusion for up to an hour or as continuous infusion for up to 96 hours.

The solution is given via the tubing of a freely running intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection within 2 to 15 minutes. This technique minimises the risk of thrombophlebitis or perivenous extravasation, which can lead to severe local cellulites, vesication and tissue necrosis. A direct intravenous injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Intravenous administration:
The dosage of doxorubicin depends on dosage regimen, general status and previous treatment of the patient. Dose schedule of doxorubicin hydrochloride administration could vary according to indication (solid tumors or acute leukemia) and according to its use in the specific treatment regimen (as single agent or in combination with other cytotoxic agents or as a part of multidisciplinary procedures that include combination of chemotherapy, surgical procedure and radiotherapy and hormonal treatment).

Monotherapy
Dosage is usually calculated on the basis of body surface area (mg/m^2). On this basis, a dose of 60 - 75 mg/m^2 body surface area is recommended every three weeks when doxorubicin is used as a single agent.

Combination regimen
When doxorubicin hydrochloride is administered in combination with other antitumour agents with overlapping toxicity, such as high-dose i.v. cyclophosphamide or related anthracycline compounds such as daunorubicin, idarubicin and/or epirubicin, the dosage of doxorubicin should be reduced to 30-60 mg/m^2 every 3 – 4 weeks.

In patients, who cannot receive the full dose (eg. in case of immunosuppression, old age), an alternative dosage is 15-20 mg/m^2 body surface per week.

Intravesical administration:
Doxorubicin may be used by intravesical instillation for the treatment of superficial bladder carcinoma or in prophylaxis of tumor recurrence after transurethral resection (T.U.R) in patients with high risk of recurrence. The recommended doxorubicin hydrochloride dose for local intravesical treatment of superficial bladder tumors is instillation of 30-50 mg in 25-50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. The optimal concentration is about 1 mg/ml. Generally the solution should be retained intravesically for 1 to 2 hours. During this period the patient should be turned 90° every 15 minutes. The patient should not drink fluids for 12 hours prior to the treatment to avoid undesired dilution with urine (this should reduce the production of urine to about 50 ml/h). The instillation may be repeated with an interval of 1 week to 1 month, dependent on whether the treatment is therapeutic or prophylactic.

Patients with impaired hepatic function
Since doxorubicin hydrochloride is mainly excreted via liver and bile, the elimination of the medicinal product may be decreased in patients with hepatic function impairment or bile flow obstruction and this could result in severe secondary effects.

General dose adjustment recommendations in patients with hepatic function impairment are based on serum bilirubin concentration:

Serum bilirubin	**Recommended dose**
20-50 micro mole/L	½ normal dose
> 50 micro mole/L	¼ normal dose

Doxorubicin is contraindicated in patients with severe liver function disorder (see section 4.3).

Patients with impaired renal function
In patients with renal insufficiency (GFR < 10 ml/min), only 75% of the planned dose should be given.

In order to avoid cardiomyopathy, it is recommended that the cumulative total lifetime dose of Doxorubicin (including related drugs such as daunorubicin) should not exceed 450-550mg/m^2 body surface area. If a patient with concomitant heart disease receives mediastinal **and/or heart irradiation, prior treatment with alkylating agents, and high-risk patients (with arterial hypertension since > 5 years, with prior coronary, valvular or myocardial heart damage, age over 70 years)** with a maximum total dose of 400 mg/m^2 body surface area should not be exceeded and the cardiac function of these patients should be monitored (see section 4.4).

Dose in children
Dosage in children may need to be reduced, please refer to treatment protocols and the specialist literature.

Obese patients
A reduced starting dose or prolonged dose interval might need to be considered in obese patients (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance doxorubicin hydrochloride or to any of the excipients

Contraindications for intravenous administration:
- Hypersensitivity to anthracendiones or other anthracyclines
- Marked persisting myelosuppression and/or severe stomatitis induced by previous treatment with other cytotoxic agents and/or radiation
- Previous treatment with anthracyclines up to their maximum cumulative dose
- Generalized infection
- Severe impaired liver function
- Severe arrhythmias, heart failure, previous myocardial infarction, acute inflammatory heart disease
- Increased haemorrhagic tendency
- Breast-feeding (see section 4.6)

Contraindications for intravesical administration:
- Invasive tumors that have penetrated the bladder (beyond T1)
- Bladder inflammation
- Haematuria
- Difficult urinary catheter introduction (e.g. in large intravesical tumors)
- Breast-feeding (see section 4.6)
- Urinary tract infections

Doxorubicin may not be given during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Doxorubicin Injection should be administered only under the supervision of a qualified physician experienced in cytotoxic therapy for i.v. or intravesical use. Doxorubicin hydrochloride may potentiate the toxicity of other anticancer therapies. A careful control of possible clinical complications should be performed, particularly in elderly patients, in patients with a history of heart disease, or with bone-marrow suppression, or patients who previously have been treated with anthracyclines, or treated with radiation in the mediastinum.

Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring. It could be recommended therefore, that patients be hospitalised at least during the first phase of treatment. Doxorubicin may cause infertility during the time of drug administration.

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

Before or during treatment with doxorubicin the following monitoring examinations are recommended (how often these examinations are done will depend on the general condition, the dose and the concomitant medication):

- radiographs of the lungs and chest and ECG
- regular monitoring of heart function (LVEF by e.g. ECG, UCG and MUGA scan)
- daily inspection of the oral cavity and pharynx for mucosal changes
- blood tests: haematocrit, platelets, differential white cell count, SGPT, SGOT, LDH, bilirubin, uric acid.

Treatment control
Prior to start of 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, (see section 4.4).

Control of the left ventricular function
Analysis of 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 (see section 4.4).

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 symptoms generally indicate acute transient toxicity. 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 hydrochloride should be carefully considered.

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/m2. Thereafter, the risk of developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2. 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 medicinal products with the ability to suppress cardiac contractility, including cyclophosphamide and 5-fluoruracil), cardiotoxiciry with doxorubicin may occur at lower cumulative doses and cardiac function should be carefully monitored.
It is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive.

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).

Haematologic Toxicity
Doxorubicin may produce myelosuppression (See Section 4.8) Haetnatologic 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. Dose reduction or increase of the dose interval should be considered if the blood values are not normalised. 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 (including doxorubicin). Secondary leukaemia is more common when such medicinal products are given in combination with other DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic medicinal products or when doses of the anthracyclines have been escalated. These leukaemias can have a 1 to 3 year latency period.

Intravesical administration
Intravesical administration of doxorubicin may cause symptoms of chemical cystitis (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall). Special attention is needed in case of catheter problems (i.e. urethral obstruction caused by invasion of intravesical tumour). Intravesical administration is contraindicated for tumours that have penetrated the bladder (beyond T1).

Tile intravesical route of administration should not be attempted in patients with, invasive tumours that have penetrated the bladder wall, urinary tract infections, and inflammatory conditions of the bladder.

Control of serum uric acid:
During therapy serum uric acid may increase. In case of hyperuricemia antihyperuricemic therapy should be initiated.

In patients with severely impaired renal function dose reductions may be necessary (see section 4.2).

Gastrointestinal effects
An antiemetic prophylaxis is recommended.
Note: Doxorubicin should not be used in the presence in inflammations, ulcerations or diarrhoea.

Extravasation
Perivenous misinjection results in local necrosis and thrombophlebitis. A burning sensation in the region of the infusion needle is indicative of perivenous administration. If extravasation occurs, the infusion or injection has to be stopped at once; the needle should be left in place for a short time and then be removed after short aspiration. In case of extravasation start intravenous infusion of dexrazoxane, no later than 6 hours after extravasation (see the SmPC of dexrazoxane for dosing and further information). In case dexrazoxane is contraindicated, it is recommended to apply 99% dimethylsulfoxide (DMSO) locally to an area twice the size of the area concerned (4 drops to 10 cm^2 of skin surface area) and to repeat this three times a day for a period of no less than 14 days. If necessary, debridement should be considered. Because of the antagonistic mechanism, the area should be cooled after the application of DMSO (vasoconstriction vs. vasodilatation), e.g., to reduce pain. Do not use DMSO in patients who are receiving dexrazoxane to treat anthracycline-induced extravasation. Other measures have been treated controversially in the literature and have no definite value.

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 hydrochloride 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.

Infertility
Doxorubicin can have genotoxic effects. Doxorubicin may cause infertility during the time of drug 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.

Anticancer therapies:
Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have 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 (see section 4.8).

Vaccines:
This medicinal product is generally not recommended in combination with live, attenuated vaccines. Contact to persons recently vaccinated against polio should be avoided.

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

Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-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 alkalinization, and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumour lysis syndrome.

A stinging or burning sensation at the site of administration may signify a small degree of extravasation. 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.

Doxorubicin hydrochloride 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.

4.5 Interaction with other medicinal products and other forms of interaction

Doxorubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-fluorouracile, cyclophosphamide or paclitaxel) or with products affecting cardiac function (like calcium antagonists), When doxorubicin is used together with the above mentioned agents, cardiac function must be followed carefully.

The use of trastuzumab in combination with anthracyclines (such as doxorubicin) 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. If possible, there should be a sufficiently long interval (up to 22 weeks) between the end of a therapy with trastuzumab and the beginning of the anthracycline therapy. Careful monitoring of the cardiac function is imperative.

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.

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.

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.

Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while the concomitant administration of phenytoin may result in lower plasma phenytoin levels.
Elevated serum doxorubicin concentrations were reported after the concomitant administration of doxorubicin and ritonavir.

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

Clozapine may increase the risk and severity of the hematologic toxicity of Doxorubicin.

Marked nephrotoxicity of Amphotericin B can occur during doxorubicin therapy.

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.

Doxorubicin is a potent, radio sensitizing agent ("radio sensitizer"), 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. This applies also to concomitant therapies with cardiotoxic or hepatotoxic drugs.

Doxorubicin may cause exacerbations of hemorrhagic cystitis caused by previous cyclophosphamide therapy.

Doxorubicin therapy may lead to increased serum uric acid, therefore dose adjustment of uric acid lowering agents may be necessary.

Doxorubicin may reduce oral bioavailability of digoxin.

During treatment with Doxorubicin patients should not be actively vaccinated and also avoid contact with recently polio vaccinated persons.

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. In animals studies, doxorubicin has shown embryo-, foeto- and teratogenic effects (see section 5.3) and also proved to be highly mutagenic in the Ames test. Doxorubicin hydrochloride is contraindicated in pregnancy. In general, cytostatics should only be administered during pregnancy on strict indication, and the benefit to the mother weighed against possible hazards to the foetus.

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 have to use effective contraception during doxorubicin therapy and 6 months after treatment.

Lactation
Doxorubicin has been reported to be excreted in human breast milk. A risk to the suckling child cannot be excluded. Since the use of doxorubicin hydrochloride during breast-feeding is contraindicated, breast-feeding should be discontinued during treatment with doxorubicin (see section 4.3).

4.7 Effects 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

Treatment with doxorubicin often causes undesirable effects, and some of these effects are serious enough to entail careful monitoring of the patient. The frequency and kind of undesirable effects are influenced by the speed of administration and the dosage. Bone-marrow suppression is an acute dose limiting adverse effect, but is mostly transient. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death. Nausea and vomiting as well as alopecia are seen in almost all patients.

The following adverse events have been reported in association with doxorubicin therapy:

Frequencies are defined using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

	Common	**Uncommon**	**Rare**	**Not known**
Infections and infestations	Sepsis, septiciaemia			
Neoplasms benign and malignant			Secondary leukaemia when in combination with anti-neoplastic drugs which damage the DNA. (see section 4.4), tumour lysis syndrome	
Blood and lymphatic system disorders:	bone-marrow suppression, leucopenia and neutropenia			Thrombocytopenia, anaemia
Immune System disorders			Anaphylactic reactions	
Endocrine disorders				Hot flushes
Eye disorders			Conjunctivitis	
Cardiac disorders	cardiomyopathy, (2%: e.g. decrease of LVEF. dyspnoea); ECG changes (e.g. sinus tachycardia, tachyarrhythmia, ventricular tachycardia, bradycardia, bundle branch block)			arrhythmia, heart failure

Vascular disorder's		phlebitis		Thrombophlebitis; thromboembolism
Gastrointestinal disorders	nausea: vomiting; mucositis; anorexia: diarrhoea	Gastrointestinal haemorrhage, abdominal pain: ulceration of the mucous membranes in the mouth, pharynx , oesophagus and gastrointestinal tract may appear in combination with cytarabine, ulceration and necrosis of the colon, in particular the caecum, have been reported (see section 4.5)		
Respiratory, thoracic and mediastinal disorders				Bronchospasm, radiation pneumonitis
Skin and subcutaneous tissue disorder's:	alopecia	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	tissue hypoxia
Renal and urinary disorders:	local reactions (chemical cystitis) might occur at intravesical treatment (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall)			acute renal failure, hyperuricaemia (see section 4.4)
Reproductive system and breast disorders				Amenorrhoea, oligospermia, azoospermia (see section 4.4)
General disorders and administration site conditions:		dehydratation	anaphylactic reactions, shivering, fever, dizziness	A stinging or burning sensation at the administration site (see section 4.4) Malaise/weakness
Hepatobiliar disorders				Hepatotoxicity, transient increase of liver enzymes

Surgical and medical procedure				Extravasation can lead to severe cellulitis, vesication and local tissue necrosis which may require surgical measures (including skin grafts) (see section 4.4)

4.9 Overdose

Acute overdosage of doxorubicin may lead to myelosuppression (particularly leucopenia and thrombocytopenia), generally 10 - 14 days following overdose, gastrointestinal toxic effects (particularly mucositis) and acute cardiac alterations, which may occur within 24 hours. Treatment includes intravenous antibiotics, transfusion of granulocytes and thrombocytes and treatment of the gastrointestinal symptoms and heart effects. Moving the patient to a sterile room and the use of a haemopoietic growth factor should be considered.

Single doses of 250 mg and 500 mg of doxorubicin have proved fatal.

Chronic overdosage, with a cumulative dose exceeding 550 mg/m^2 increases the risk for cardiomyopathy and may lead to heart failure, which should be treated along conventional lines.

Delayed cardiac failure may occur up to six months after the overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances
ATC code: L01DB01

Doxorubicin is an anthracycline antibiotic. The mechanism of action is not completely elucidated. It is postulated that doxorubicin hydrochloride 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 all 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 $OH^{\bullet}$. 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 cardiotoxic effects.

5.2 Pharmacokinetic properties

Distribution
Following intravenous injection, doxorubicin is rapidly cleared from the blood and widely distributed into tissues including lungs, liver, heart, spleen, lymph nodes, bone marrow and kidneys. The volume of distribution is about 25 litres. The degree of protein binding is 60-70%.

Doxorubicin does not cross the blood-brain barrier, although higher levels in liquor may be reached in the presence of brain metastases or leukemic cerebral dissemination. Doxorubicin is rapidly distributed into the ascites, where it reaches higher concentrations than in plasma. Doxorubicin is secreted into breast milk.

Elimination
The elimination of doxorubicin from the blood is triphasic with mean half-lives of 12 minutes (distribution), 3.3 hours and about 30 hours. Doxorubicin undergoes rapid metabolism in the liver. The main metabolite is the pharmacologically active doxorubicinol. Other metabolites are deoxyrubicin aglycone, glucuronide and sulphate conjugate. About 40 to 50% of a dose is excreted in bile within 7 days, of which about half is excreted as unchanged drug and the rest as metabolites. Only 5-15% of the administered dose is eliminated in urine.

Special populations
As the elimination of doxorubicin is mainly hepatic, impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Dose reduction is generally advised.

Although renal excretion is a minor elimination pathway for doxorubicin, severe renal impairment might affect total elimination and require dose reduction.

In a study in obese patients (>130% of ideal bodyweight) the doxorubicin clearance was reduced and the half life increased compared with a normal-weight control group. Dose adjustments might be necessary in the obese.

5.3 Preclinical safety data

Animal studies from literature show that Doxorubicin affects the fertility, is embryo- and foetotoxic and teratogenic. Other data shows that Doxorubicin is mutagenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid (for pH adjustment)

Water for injections

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.

Until detailed compatibility information about miscibility is available, Doxorubicin should not be mixed with other medicinal products than those mentioned under section 6.6.

6.3 Shelf life

Unopened vials: 18 months

Opened vials: The product should be used immediately after opening the vial.

Prepared infusion solutions:
Chemical and physical in-use stability has been demonstrated in 0.9% sodium chloride injection and 5% dextrose injection for up to 28 days at 2 – 8°C and for up to 7 days at 25°C when prepared in glass containers-protected from light.

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 and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic condition.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

For 5 ml,
Concentrate for solution for infusion is filled in 5 ml Type - I clear tubular glass vial closed with chlorobutyl rubber stopper with teflon coating and aluminium flip off pink seal.

For 25 ml,
Concentrate for solution for infusion is filled in 30 ml Type - I clear molded glass vial closed with chlorobutyl rubber stopper with teflon coating and aluminium flip off pink seal.

For 100 ml,
Concentrate for solution for infusion is filled in 100 ml Type - I clear molded glass vial closed with chlorobutyl rubber stopper with teflon coating and aluminium flip off pink seal.

Pack sizes:
1 × 5 ml vial
1 × 25 ml vial
1 × 100 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Doxorubicin is a potent cytotoxic agent which should only be prescribed, prepared and administered by professionals who have been trained in the safe use of the preparation. The following guidelines should be followed when handling, preparing and disposing of doxorubicin.

Preparation
1. Personnel should be trained in good technique for handling.
2. Pregnant staff should be excluded from working with this drug.
3. Personnel handling doxorubicin should wear protective clothing: goggles, gowns, disposable gloves and masks.
4. All items used for administration or cleaning, including gloves, should be placed in high risk waste disposal bags for high temperature (700°C) incineration.
5. All cleaning materials should be disposed of as indicated previously.
6. Always wash hands after removing gloves.

Contamination
1. In case of contact with skin or mucous membrane, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not graze the skin by using a scrubbing brush. A bland cream may be used to treat transient stinging of skin.
2. 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 or normal sodium chloride 9 mg/ml (0.9%) solution for injection. Then seek medical evaluation by a physician or eye specialist.
3. In the event of spillage or leakage treat with 1% sodium hypochlorite solution or most simply with phosphate buffer (pH>8) until solution is destained. Use a cloth/sponge kept in the designate area. Rinse twice with water. Put all cloths into a plastic bag and seal for incineration.

Administration:
Intravenous (IV) administration of Doxorubicin must be very careful and it is advisable to give the medicinal product via the tubing of a freely running intravenous sodium chloride 9 mg/ml (0.9%) or dextrose 50 mg/ml (5%) within 2 to 15 minutes. This method minimizes the risk of thrombosis development and perivenous extravasation that result in severe cellulitis, vesication and tissue necrosis, and also provides rinse of the vein after the administration.

Remnants of the medicinal product as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste.

Disposal
Single use only. Any unused product or waste material should be disposed of in accordance with local requirements. Observe guidelines for handling cytotoxic drugs.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0109

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/03/2010

10 DATE OF REVISION OF THE TEXT

12/03/2010

Module 3

Product Information Leaflet

accord

PACKAGE LEAFLET: INFORMATION FOR THE USER

Doxorubicin 2 mg/ml Concentrate for Solution for Infusion

Doxorubicin hydrochloride

Read all of this leaflet carefully before you start using this medicine
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Doxorubicin concentrate for solution for infusion is and what it is used for

The name of your medicine is "Doxorubicin 2 mg/ml Concentrate for Solution for Infusion" but in the rest of the leaflet it will be called 'Doxorubicin concentrate for solution for infusion'.

Doxorubicin is one of a group of medicines called the anthracyclines. These drugs are also known as cancer drugs, chemotherapy, or "chemo". They are used in the treatment of various cancers to slow or stop the growth of cancer cells. A combination of different types of cancer drugs will often be used to achieve better results and minimize side effects.
Doxorubicin concentrate for solution for infusion is used to treat the following forms of cancer:
- breast cancer
- cancer of the connective tissue, ligaments, bone, muscle (sarcoma)
- cancer develops within the stomach or intestine
- lung cancer
- lymphomas, a cancer affecting the immune system
- leukaemia, a cancer that causes abnormal production of blood cell
- cancer of the thyroid gland
- advance ovarian and endometrial cancer (a cancer of the lining of the uterus or of the uterus)
- bladder cancer
- advance neuroblastoma (a cancer of the nerve cells commonly found in children)
- malignant renal tumour in children (Wilm´s tumour)
- myeloma (cancer of the bone marrow)

2. Before you are given Doxorubicin concentrate for solution for infusion

You should not be given Doxorubicin concentrate for solution for infusion
- if you are allergic (hypersensitive) to Doxorubicin hydrochloride or any of the other ingredients of the Doxorubicin concentrate for solution for infusion or to other anthracycline.
- if you have been told your blood is thin (your bone marrow is not working well).
- if you have received doxorubicin, other anthracyclines, other anti-tumour drugs or immunosuppressive drugs before.

The following information is intended for medical or healthcare professionals only

Posology and method of administration
Doxorubicin Injection should be administered only under the supervision of a qualified physician with extensive experience in cytotoxic treatment. Also, patients must be carefully and frequently monitored during the treatment.
Due to the risk of often lethal cardiomyopathy, the risks and benefits of the individual patient should be weighted before each application.
Doxorubicin is administered intravenously and intravesically and must not be administered orally, subcutaneously, intramuscularly or intrathecally. Doxorubicin can be administered intravenously as bolus within minutes, as short infusion for up to an hour or as continuous infusion for up to 96 hours.
The solution is given via the tubing of a freely running intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection within 2 to 15 minutes. This technique minimises the risk of thrombophlebitis or perivenous extravasation, which can lead to severe local cellulites, vesication and tissue necrosis. A direct intravenous injection is not recommended due

- if you tend to bleed easily.
- if you suffer from any kind of infection.
- if you suffer from mouth ulcers.
- if your liver is not working well.
- if you suffer from an infection of the bladder (in case the medicine is given to you by an administration in to your bladder).
- if there is blood in your urine
- had a heart attack
- impaired heart function
- serious abnormality of the heart beat (arrhythmia)

You should not receive the medicine through a catheter (a thin flexible tube) into your bladder if you have:
- a tumour that has grown into the bladder wall
- an urinary tract infection
- bladder inflammation
- problems with the insertion of a catheter

Take Special care with Doxorubicin concentrate for solution for infusion
Please tell your doctor if you have or have had any of the following medical conditions or illnesses:
- poor blood cell production in the bone marrow
- heart problems
- liver disorders
- kidney disorders

You should also tell your doctor:
- if you have ever received doxorubicin or any similar anti-cancer medicine (anthracycline) for the treatment of cancer
- if you have received radiation treatment to the upper body

Before starting and during treatment with Doxorubicin concentrate for solution for infusion your doctor will perform the following tests:
- blood counts
- function tests of your heart, liver and kidney

Doxorubicin strongly reduces blood cell production in the bone marrow. This may make you more prone to infections or bleeding. It should be made sure that severe infections and/or bleedings can be treated without delay and efficaciously.

Tell your doctor immediately:
- if you feel a stinging or burning pain at the site of injection. Such a pain can occur if the medicine leaks out of the vein.

Your doctor will monitor your heart function carefully during the treatment because:
- doxorubicin may damage the heart muscle
- doxorubicin treatment may lead to heart failure after a certain cumulative dose (adding up of single doses)
- the risk for a heart muscle damage is higher if you have previously received medicines that may damage the heart or radiotherapy of the upper body.

The levels of uric acid (showing that cancer cells are destroyed) in your blood may be high during treatment. Your doctor will tell you if you need to take any medicine to control this.
- Existing infections should be treated before Doxorubicin concentrate for solution for infusion therapy is started.
- This medicinal product is generally not recommended in combination with live, attenuated vaccines. Contact to persons recently vaccinated against polio should be avoided.
- As Doxorubicin concentrate for solution for infusion is excreted mainly via the liver and in the bile, its excretion can be reduced if liver function is impaired or the bile ducts narrowed, and this can lead to severe secondary side effects.

Doxorubicin concentrate for solution for infusion can turn the urine red. This is not a sign of damage to health.

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to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.
Intravenous administration:
The dosage of doxorubicin depends on dosage regimen, general status and previous treatment of the patient. Dose schedule of doxorubicin hydrochloride administration could vary according to indication (solid tumours or acute leukaemia) and according to its use in the specific treatment regimen (as single agent or in combination with other cytotoxic agents or as a part of multidisciplinary procedures that include combination of chemotherapy, surgical procedure and radiotherapy and hormonal treatment).
Monotherapy
Dosage is usually calculated on the basis of body surface area (mg/m²). On this basis, a dose of 60 - 75 mg/m² body surface area is recommended every three weeks when doxorubicin is used as a single agent.
Combination regimen
When doxorubicin hydrochloride is administered in combination with other antitumour agents with overlapping toxicity, such as high-dose i.v. cyclophosphamide or related anthracycline compounds such as daunorubicin, idarubicin and/or epirubicin, the dosage of doxorubicin

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The following medications can interact with Doxorubicin 2 mg/ml concentrate for solution for infusion:
- Other cytostatics (medication against cancer) e.g. anthracyclines (daunorubicin, epirubicin, idarubicin, trastuzumab), cisplatin, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, dactinomycin, fluorouracil, mitomycin C, taxanes (e.g. paclitaxel), mercaptopurine, methotrexate, streptozocin
- Cardioactive drugs (medication to treat heart diseases) e.g. calcium channel blockers, verapamil, and digoxin
- Medicines that lower the uric acid level in your blood
- Inhibitors of cytochrome P-450 (drugs that stop the substance cytochrome P-450, which is a important for detoxification of your body, from working: e.g. cimetidine), drugs inducing cytochrome P–450 (e.g. rifampicin, barbiturates including phenobarbital)
- Antiepileptic drugs (e.g. carbamazepine, phenytoin, valproate)
- Heparin (prevents the clotting of blood)
- Antiretroviral drugs (medication against special forms of viruses).
- Chloramphenicol and sulphonamides (medication against bacteria)
- Progesterone (e.g. at threatening miscarriage)
- Amphotericin B (drugs used against fungal diseases)
- Live vaccines (e.g. polio (myelitis), malaria)

Please note that this can also apply to recently used medicines.

Pregnancy and breast-feeding
Pregnancy
It is known that doxorubicin passes through the placenta and harms the foetus in animal experiments. If you are pregnant, your doctor will give you doxorubicin only if the benefits of the treatment outweigh the potential harm for the unborn child. Tell your doctor immediately if you are pregnant or think you are pregnant.

If you are a woman, you should not get pregnant during treatment with doxorubicin or up to 6 months after treatment.
If you are a man, you should take adequate precautions to ensure that your partner does not become pregnant during your treatment with doxorubicin or 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.
If you are considering becoming parents after the treatment please discuss this with your doctor.

Breast-feeding
Do not breast-feed while you are treated with Doxorubicin concentrate for solution for infusion. The medicine can be passed on to the baby through the breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

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

Important information about some of the ingredients of Doxorubicin concentrate for solution for infusion
This medicinal product contains 0.15 mmol (3.5 mg) sodium per ml. To be taken into consideration by patients on a Controlled sodium diet.

3. How Doxorubicin concentrate for solution for infusion is given

Method and routes of administrations
Doxorubicin concentrate for solution for infusion can only be given under supervision by a doctor with experience in cancer treatment.
Dosage: Your doctor will decide about the dose you will receive.

should be reduced to 30-60 mg/m² every 3 – 4 weeks.
In patients, who cannot receive the full dose (eg. in case of immunosuppression, old age), an alternative dosage is 15-20 mg/m² body surface per week.
Intravesical administration:
Doxorubicin may be used by intravesical instillation for the treatment of superficial bladder carcinoma or in prophylaxis of tumour recurrence after transurethral resection (T.U.R) in patients with high risk of recurrence. The recommended doxorubicin hydrochloride dose for local intravesical treatment of superficial bladder tumours is instillation of 30-50 mg in 25-50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. The optimal concentration is about 1 mg/ml. Generally the solution should be retained intravesically for 1 to 2 hours. During this period the patient should be turned 90° every 15 minutes. The patient should not drink fluids for 12 hours prior to the treatment to avoid undesired dilution with urine (this should reduce the production of urine to about 50 ml/h). The instillation may be repeated with an interval of 1 week to 1 month, dependent on whether the treatment is therapeutic or prophylactic.
Patients with impaired hepatic function
Since doxorubicin hydrochloride is mainly excreted via liver and bile,

Do not administer the medicine your self. Your medicine will be given to you as part of an intravenous infusion, into a blood vessel, under the direction of specialists. You will be monitored regularly both during and after your treatment. If you suffer from superficial bladder cancer it is possible that you may receive your medicine into your bladder (intravesical use).

Dosage

The Dosage is usually calculated on the basis of your body surface area. 60-75 mg per square metre of body surface area may be given every 3 weeks when used alone. The dosage may need to be reduced to 30-60 mg per square metre of body surface area and the treatment interval prolonged when given in combination with other anti-tumour drugs. Your doctor will advise you of how much you will need. If given weekly the recommended dose is 15 - 20 mg per square metre of body surface area. Your doctor will advise you of how much you will need.

Patients with reduced liver and renal functions

If liver or kidney function is reduced, the dosage should be decreased. Your doctor will advise you of how much you will need.

Children/elderly or patients after radiotherapy

The dosage may need to be reduced in children and the elderly or if you have received any radiotherapy. Your doctor will advise you or how much you need.

Patient with bone marrow suppression

The dosage may need to be reduced in patient with bone marrow suppression. Your doctor will advise you of how much you need.

Obese patients

The starting dose may be reduced in obese patients or the dose interval may be prolonged. Your doctor will advise you of how much you need and how often.

If you are given more Doxorubicin concentrate for solution for infusion than you should

During and after treatment your doctor or nurse will carefully monitor you. The symptoms of an overdose are an extension of doxorubicin's possible side effects. Particularly the blood changes and heart problems. Heart disorders may even occur up to six month after you received the over dose.

In case of an overdose your doctor will take appropriate measures. Such as a blood transfusion and/or treatment with antibiotics.

Please tell your doctor if any of the symptoms occur.

If you missed a dose of Doxorubicin concentrate for solution for infusion

Your doctor will decide on the duration of your treatment with Doxorubicin concentrate for solution for infusion. If the treatment is stopped before the advised courses of treatment is finished. The effects of the doxorubicin therapy might be reduced. Ask your doctor for advice if you wish to stop the treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Doxorubicin concentrate for solution for infusion can cause side effects, although not everybody gets them.

Please contact your doctor or nurse immediately if you notice any of the following side effects:

- Feeling dizzy, feverish, short of breath with a tight chest or throat or have an itchy rash. This type of allergic reaction can be very serious.
- Anaemia (a low red blood cell count) that can leave you feeling tired and lethargic.
- White blood cell counts (Which fight infection) can also drop, increasing the chance of infections and raised temperature (fever)
- Platelets (these are cells that help the blood to clot) can be affected which could make you bruise or bleed more easily. It is important to seek medical advice if this happens. Your doctor should test your blood cell count during treatment.
- Doxorubicin may cause decreased activity in your bone marrow.

the elimination of the medicinal product may be decreased in patients with hepatic function impairment or bile flow obstruction and this could result in severe secondary effects.

General dose adjustment recommendations in patients with hepatic function impairment are based on serum bilirubin concentration:

Serum Bilirubin	Recommended Dose
20-50 micro mole/L	½ normal dose
> 50 micro mol/L	¼ normal dose

Doxorubicin is contraindicated in patients with severe liver function disorder.

Patients with impaired renal function

In patients with renal insufficiency (GFR < 10 ml/min), only 75% of the planned dose should be given.

In order to avoid cardiomyopathy, it is recommended that the cumulative total lifetime dose of Doxorubicin (including related drugs such as daunorubicin) should not exceed 450-550mg/m² body surface area. If a patient with concomitant heart disease receives mediastinal **and/or heart irradiation, prior treatment with alkylating agents, and high-risk patients (with arterial hypertension since > 5 years, with prior coronary, valvular or myocardial heart damage, age over 70 years)** with a maximum total dose of 400 mg/m² body surface

Frequency:
Very common (more than 1 in 10 patients)
Common (more than 1 in 100 patients, but less than 1 in 10 patients)
Uncommon (more than 1 in 1000 patients, but less than 1 in 100 patients)
Rare (more than 1 in 10,000 patients, but less than 1 in 1,000 patients)
Very rare (less than 1 in 10.000 patients)
Not known (can not be estimated from the available data)

Common
cardiomyopathy (heart muscle disease)
ECG (electrocardiogram) changes
bone-marrow suppression(deficiency in blood cells causing infection and bleeding)
nausea (feeling sick)
vomiting (being sick)
mucositis (inflammation of membranes in digestive tract)
anorexia (eating disorder)
diarrhoea – may result in dehydration
chemical cystitis (bladder inflammation) sometimes haemorrhagic (with blood in urine) following administration in to the bladder
alopecia (hair loss) normally reversible
sepsis (bacteria infection)
septicaemia (bacterial infection of blood)

Uncommon
Ulceration and necrosis (death of cell/tissue) of the colon (intestine) in combination with cytarabine
phlebitis
gastrointestinal bleeding
abdominal pain
local hypersensitivity reaction of the field of radiation
dehydration

Rare
secondary leukaemia (blood cancer developed after treatment for another cancer) when in combination with anti-neoplastic drugs which damage the DNA
tumour lysis syndrome (complications of having chemotherapy)
conjunctivitis (inflammation of the outermost layer of the eye)
urticaria (hives)
exanthema (type of rash)
erythematous reactions (rash-like symptoms) along the vein used for the injection
hyperpigmentation (darkened areas) of the skin and nails
onycholysis (loosening of the nails)
anaphylactic reaction (severe allergic reactions with or without shock including skin rash, pruritis (itching), (fever and chills)
shivering
fever
dizziness

Not known
Thrombophlebitis (vein inflammation under the skin)
thromoembolism (clot formed in a blood vessel)
arrhythmia (irregular heartbeat)
heart failure (loss of cardiac function)
hyperuricaemia (high uric acid level in blood)
bronchospasm (coughing or difficulty in breathing because of narrowing sudden of airways)
pneumonitis (inflammation of lung tissue)
amenorrhoea (absence of menstruation)
oligospermia (low sperm volume)
azoospermia (lack of sperm)
Anaemia (reduction of red blood cells)
A stinging or burning sensation at the administration site in relation to extravasation. Extravasation can lead to local death of calls of the tissue which may require surgical measures
Transient increase of liver enzymes

Other Side effects: Doxorubicin concentrate for solution for infusion

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area should not be exceeded and the cardiac function of these patients should be monitored.

Dose in children

Dosage in children may need to be reduced, please refer to treatment protocols and the specialist literature.

Obese patients

A reduced starting dose or prolonged dose interval might need to be considered in obese patients.

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.

Until detailed compatibility information about miscibility is available, Doxorubicin should not be mixed with other medicinal products than 0.9% sodium chloride injection and 5% dextrose injection.

Prepared infusion solutions

Chemical and physical in-use stability has been demonstrated in 0.9% sodium chloride injection and 5% dextrose injection for up to 28 days at 2 – 8 °C and for up to 7 days at 25°C when prepared in glass containers protected from light.

may cause a red colouration of the urine for one or two days after administration. This is normal and nothing to worry about.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

5. How to store Doxorubicin concentrate for solution for infusion

Keep out of the reach and sight of children.
Do not use Doxorubicin concentrate for solution for infusion after the expiry date which is stated on the vial or outer carton. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light.
Do not use Doxorubicin concentrate for solution for infusion if you notice that the solution is not clear, red and free of particles.
Single use only. Any unused product or waste material should be disposed of in accordance with local requirements. Observe guidelines for handling cytotoxic drugs.

Unopened vials: 18 months

Opened vials: The product should be used immediately after opening the vial.
Chemical and physical in-use stability has been demonstrated in 0.9% sodium chloride injection and 5% dextrose injection for up to 28 days at 2 – 8°C and for up to 7 days at 25°C when prepared in glass containers protected from light.

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 and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic condition.

6. Further information

What Doxorubicin concentrate for solution for infusion contains:
Doxorubicin concentrate for solution for infusion contains the active ingredient Doxorubicin Hydrochloride.
1 ml contains 2 mg Doxorubicin hydrochloride
Each 5 ml vial contains 10 mg of Doxorubicin hydrochloride.
Each 25 ml vial contains 50 mg of Doxorubicin hydrochloride.
Each 100 ml vial contains 200 mg of Doxorubicin hydrochloride.
The other ingredients are sodium chloride, hydrochloric acid (for pH adjustment) and water for injections.

What Doxorubicin concentrate for solution for infusion looks like and contents of the pack:
Doxorubicin concentrate for solution for infusion is a clear, red solution, which is practically free from particles.
Pack sizes:
1 × 5 ml vial
1 × 25 ml vial
1 × 100 ml vial

Not all pack sizes may be marketed.

Marketing Authorisation Holder and manufacturer:
Accord Healthcare Limited
Sage House, 319, Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

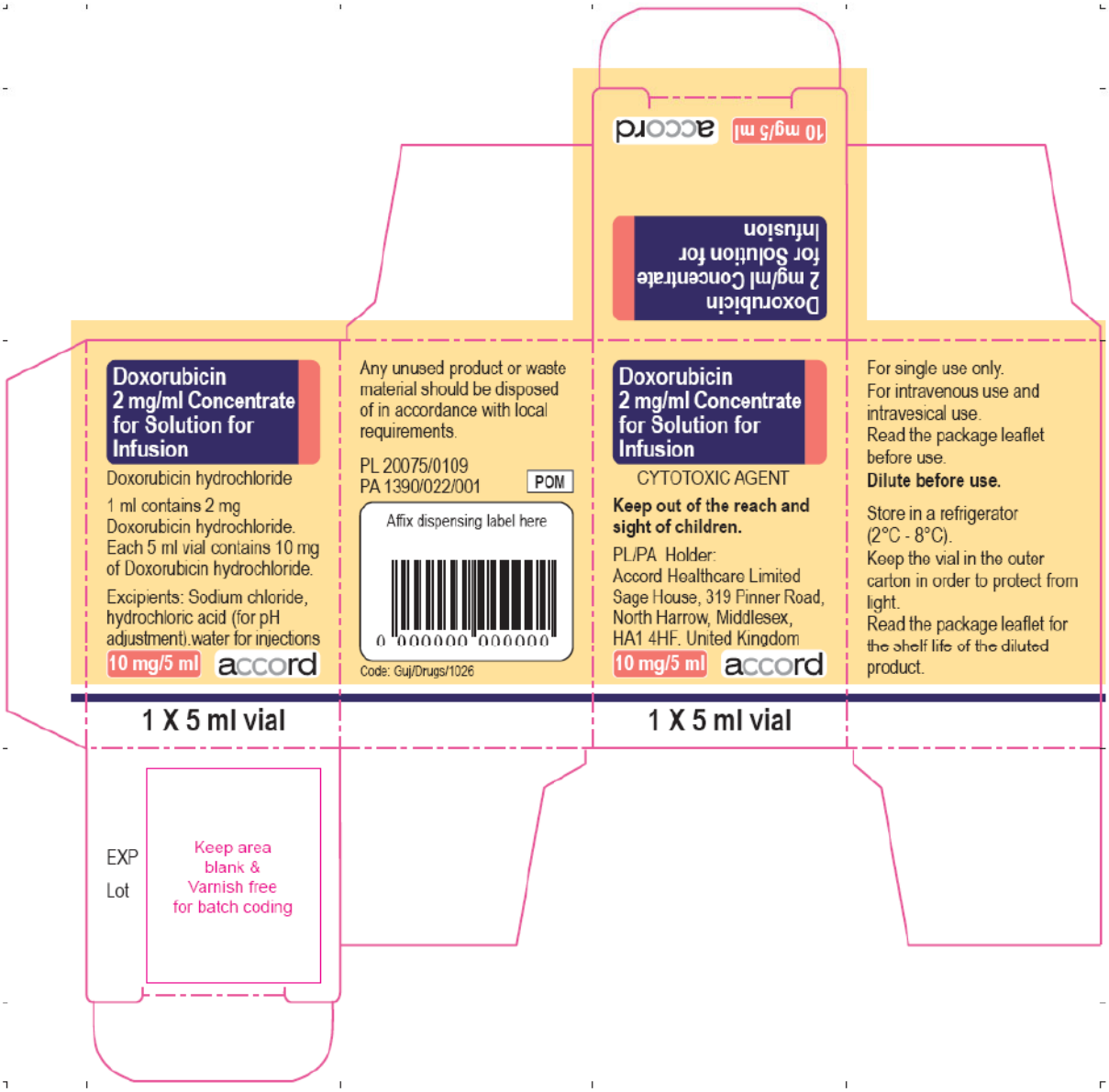
The leaflet was last approved in 02/2010.

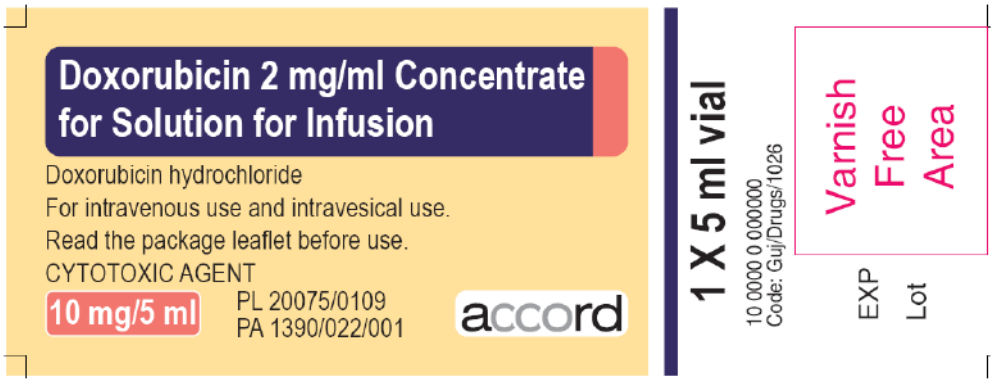
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic condition.
Disposal
Remnants of the medicinal product as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Shelf life and storage
Unopened vials: 18 months
Opened vials: The product should be used immediately after opening the vial.
Store in a refrigerator (2°C - 8°C).
Keep the vial in the outer carton in order to protect from light.

Module 4

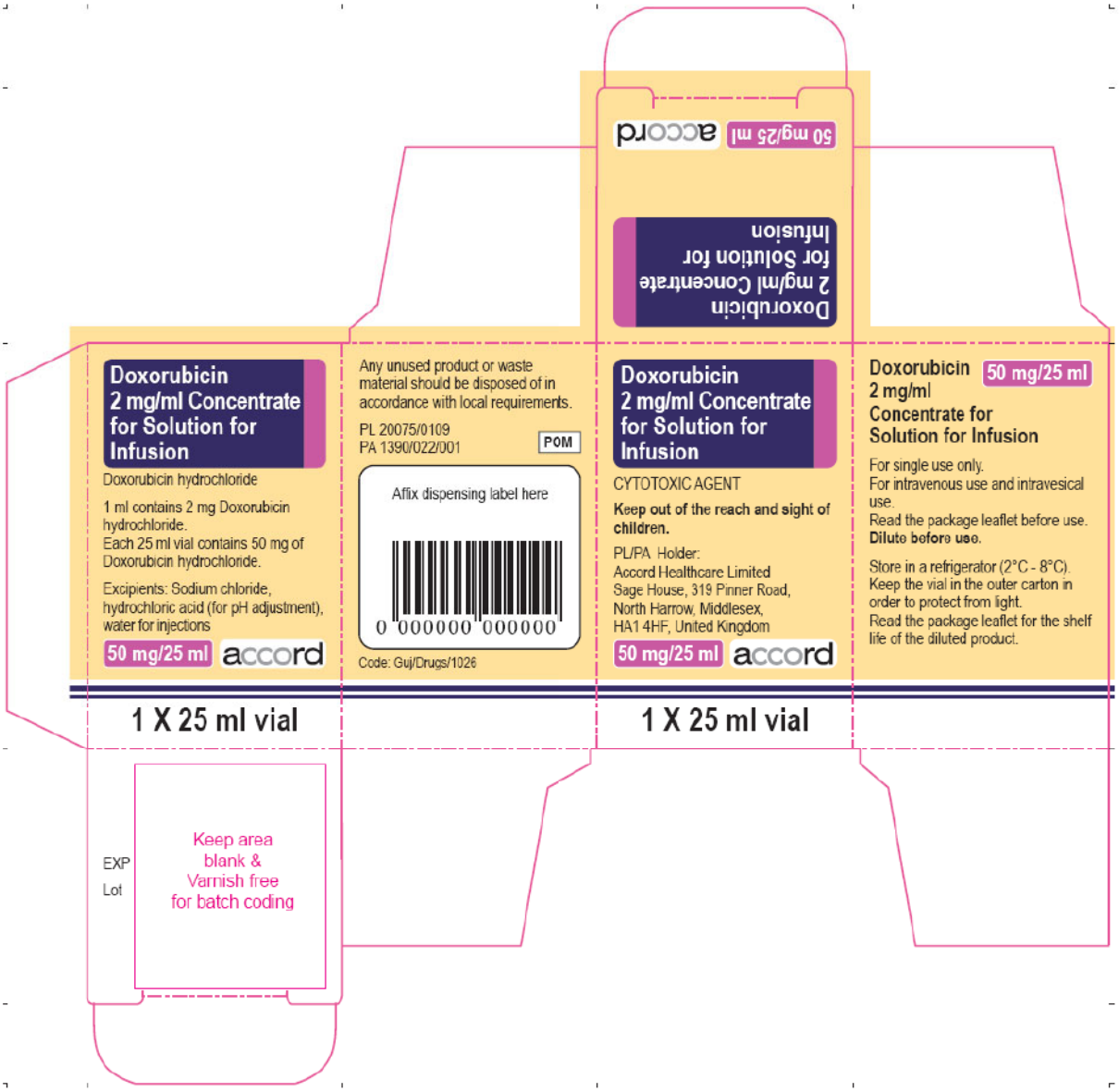
Labelling

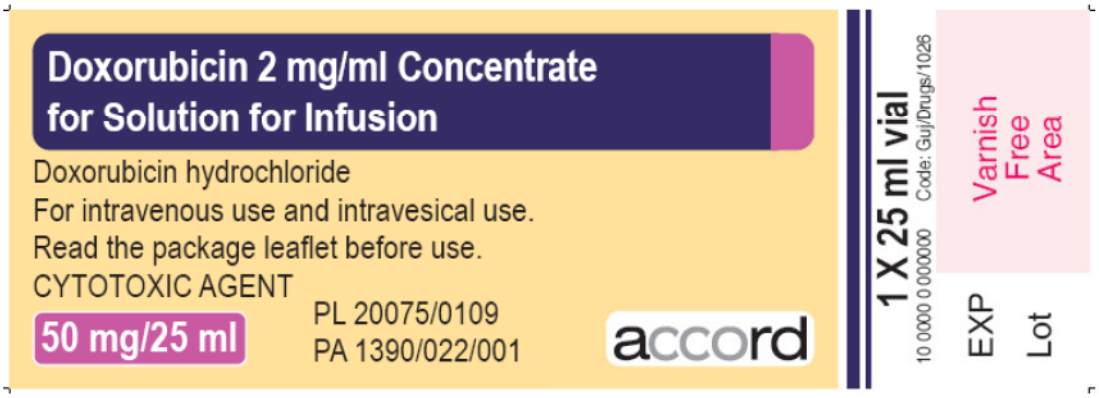
10mg/5ml presentation - carton and immediate label



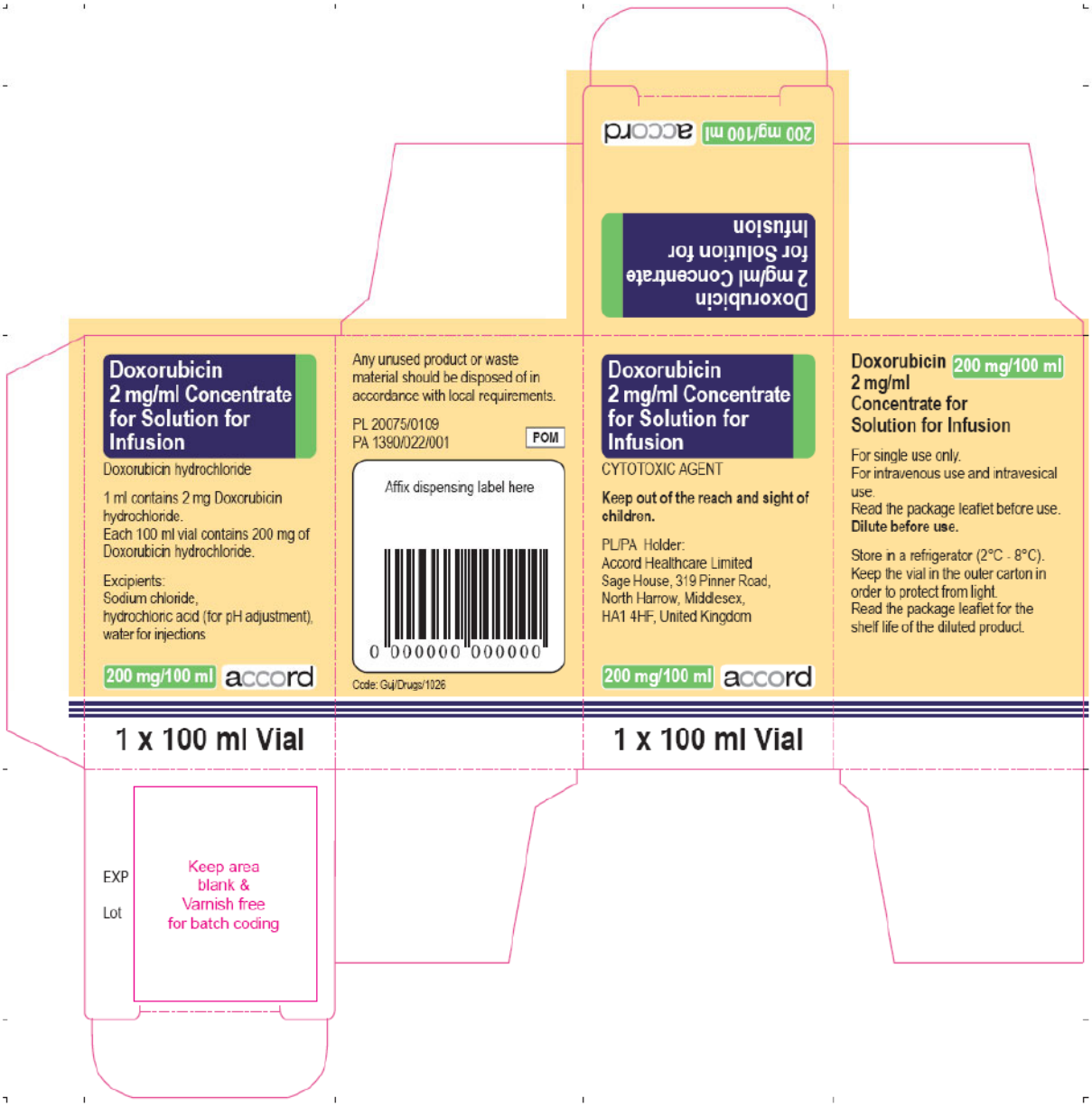


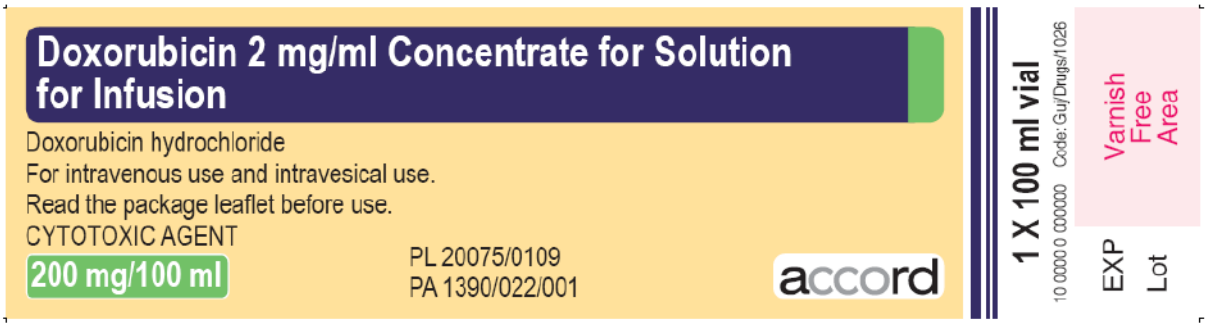
50mg/25ml presentation - carton and immediate label





200mg/100ml presentation - carton and immediate label





Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Accord Healthcare Limited a Marketing Authorisation for the medicinal product Doxorubicin 2mg/ml Concentrate for Solution for Infusion (PL 20075/0109, UK/H/1347/001/DC) on 11th March 2010. The product is a prescription-only medicine.

This is an abridged application for Doxorubicin 2mg/ml Concentrate for Solution for Infusion, submitted under Article 10.1 of 2001/83 EC, as amended, cross-referring to Doxorubicin Solution for Infusion (PL 03433/0127), authorised to Farmitalia Carlo Erba Limited in the UK on 27th November 1989. The UK reference product has been authorised in the EEA for more than 10 years, so the period of data exclusivity has expired. The innovator European reference product is Adriamycin 2mg/ml Solution for Injection, authorised to Pfizer on 12th October 1988, in Denmark. With the UK as the Reference Member State in this Decentralised Procedure, Accord Healthcare Limited applied for a Marketing Authorisation for Doxorubicin 2mg/ml Concentrate for Solution for Infusion in AT, BE, BG, DE, DK, EE, ES, FI, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE and SI.

Doxorubicin belongs to the group of anthracyclines (ATC code - L01D B01) and has broad spectrum activity against many different tumour types. It is an anti-neoplastic antibiotic isolated from *Streptomyces peucetius var. cassius*, for use in the treatment of acute leukaemias, malignant lymphomas and a large number of solid tumours, either alone or in combination with other cytotoxic drugs. The full indications and posology are detailed in the Summary of Product Characteristics (SmPC). Doxorubicin exerts its anti-neoplastic effect via cytotoxic mechanisms of action, especially intercalation into DNA, inhibition of the enzyme topoisomerase II, and formation of reactive oxygen species (ROS). The main undesirable effects of doxorubicin (like other anthracyclines) are bone marrow depression (myelosuppression), mucositis, severe local tissue damage after extravasation, cardiac toxicity and alopecia. An important cause of treatment failure with doxorubicin and other anthracyclines is the development of resistance.

Following intravenous injection, doxorubicin is rapidly cleared from the blood and widely distributed into tissues including lungs, liver, heart, spleen, lymph nodes, bone marrow and kidneys. The volume of distribution is about 25 litres. The degree of protein binding is 60-70%. The elimination of doxorubicin from the blood is triphasic with mean half-lives of 12 minutes (distribution), 3.3 hours and about 30 hours. Doxorubicin undergoes rapid metabolism in the liver. The main metabolite is the pharmacologically active doxorubicinol. About 40 to 50% of a dose is excreted in bile within 7 days, of which about half is excreted as unchanged drug and the rest as metabolites. Only 5-15% of the administered dose is eliminated in urine.

The drug product is presented as a clear, red concentrate for solution for infusion. It is diluted with either 0.9 % sodium chloride solution or 5 % dextrose solution to give the solution for infusion. This medicine is not for self-administration; it will be administered to the patient by a healthcare professional.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is for a generic version of an approved product and it is not likely to change the total market of doxorubicin.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Doxorubicin 2mg/ml Concentrate for Solution for Infusion
Name(s) of the active substance(s) (INN)	Doxorubicin hydrochloride
Pharmacotherapeutic classification (ATC code)	Anthracyclines and related substances (L01D B01)
Pharmaceutical form and strength(s)	Concentrate for solution for infusion (2 mg / ml)
Reference numbers for the Mutual Recognition Procedure	UK/H/1347/001/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, BG, DE, DK, EE, ES, FI, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE and SI
Marketing Authorisation Number(s)	PL 20075/0109
Name and address of the authorisation holder	Accord Healthcare Limited Sage House, 319, Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

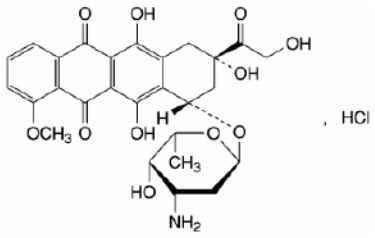
ACTIVE SUBSTANCE

Doxorubicin hydrochloride

Nomenclature:

INN:	Doxorubicin hydrochloride
Chemical names:	(20*S*)-7-Ethyl-10-[4-(1-piperidino-1-piperidino)]carbonyloxycamptothecin hydrochloride trihydrate

Structure:



Molecular formula:	$C_{27}H_{29}NO_{11}$. HCl
Molecular weight:	579.99 g/mol
CAS No:	25316-40-9
Physical form:	Orange-red, crystalline powder, hygroscopic
Solubility:	Soluble in water, slightly soluble in methanol, practically insoluble in acetone and in methanol

The active substance, doxorubicin hydrochloride, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of doxorubicin hydrochloride are supported by an EDQM Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of doxorubicin hydrochloride for inclusion in this medicinal product.

The current CEP states a re-test period of 24 months when the active is stored in brown type III glass containers with polypropylene caps and polyethylene cap inserts.

DRUG PRODUCT

Other ingredients

The drug product is presented as a clear, red concentrate for solution for infusion.

Other ingredients consist of pharmaceutical excipients, namely sodium chloride, hydrochloric acid (for pH adjustment), and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Impurity profiles

Comparative impurity profiles were provided for test and reference products and impurities were found to be lower for the test product. All impurities were within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory validation data were provided for two batches of each presentation at the proposed batch sizes. All data were within specification.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory Certificates of Analysis have been provided for two full-scale batches of each of the product presentations. All parameters are well within specification and comparable. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The drug product is licensed for marketing in colourless Type I glass vials of volume 5ml, 30ml, or 100ml, closed with chlorobutyl rubber stoppers and aluminium flip-off seals. The vials contain 5ml, 25ml, or 100ml of sterile solution of doxorubicin hydrochloride (concentration 2 mg/ml).

The vials are packaged individually with the Product Information Leaflet (PIL) into cardboard outer cartons. The licensed pack sizes are therefore 1 x 5ml, 1 x 25ml, and 1 x

100ml. The MAH has stated that not all pack sizes may be marketed. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 18 months has been set for the unopened vial, which is satisfactory. Storage conditions are 'Store in a refrigerator (2ºC - 8ºC). Keep the vial in the outer carton in order to protect from light.'. For storage conditions and advice for use of the opened vial, refer to the SmPC. Please also refer to the SmPC for information on safe handling and disposal of the product and contaminated materials.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling and PIL have been provided.

Conclusion

The proposed product, Doxorubicin 2mg/ml Concentrate for Solution for Infusion, has been shown to be a generic version of the reference product, Doxorubicin Solution for Infusion (PL 03433/0127, Farmitalia Carlo Erba Limited), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of doxorubicin hydrochloride, which is a widely used and well-known active substance. The CV of the non-clinical expert has been supplied.

III.3 CLINICAL ASPECTS

INDICATIONS

Doxorubicin 2mg/ml Concentrate for Solution for Infusion is indicated in a range of neoplastic conditions including small-cell lung cancer (SCLC), breast cancer, advanced ovarian carcinoma, intravesically for bladder cancer, neoadjuvant and adjuvant therapy of osteosarcoma, advanced soft-tissue sarcoma in adults, Ewing's sarcoma, Hodgkin's disease, Non-Hodgkin's lymphoma, acute lymphatic leukaemia, acute myeloblastic leukaemia, advanced multiple myeloma, advanced or recurrent endometrial carcinoma, Wilms' tumour, advanced papillary/follicular thyroid cancer, anaplastic thyroid cancer, and advanced neuroblastoma.

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

The indications are consistent with those for the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of doxorubicin hydrochloride is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Clinical efficacy

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. Doxorubicin is indicated in the treatment of acute leukaemias, malignant lymphomas and a large number of solid tumours including breast and lung cancer. The discussion in the clinical overview supports the view of doxorubicin as an efficacious anti-cancer agent in a variety of tumour types.

Doxorubicin 2mg/ml Concentrate for Solution for Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the currently authorised reference product Doxorubicin Solution for Infusion (Farmitalia Carlo Erba Limited). Thus, in accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

Clinical safety

No novel safety data have been submitted and none are required for applications of this type. The safety profile of doxorubicin hydrochloride is well-known. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The MAH has provided a review of clinical trials published in the literature, confirming the safety of doxorubicin.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product, and is acceptable.

Product Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.

Expert Report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Post marketing experience

No post-marketing data is available. The medicinal product has not been marketed in any country.

Periodic Safety Update Report (PSUR)

The RMS recommends PSUR submissions to be aligned with the EU Harmonised Birthday and related Data Lock Points as published on the HMA website and recommends submission of three yearly PSURs.

CONCLUSIONS & DISCUSSION

The grounds for establishing the proposed product, Doxorubicin 2mg/ml Concentrate for Solution for Infusion, as a generic version of the reference product, Doxorubicin Solution for Infusion (PL 03433/0127, Farmitalia Carlo Erba Limited), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. All issues have been adequately addressed by the applicant. When used as indicated, Doxorubicin 2mg/ml Concentrate for Solution for Infusion has a favourable benefit-to-risk ratio. The granting of a Marketing Authorisation was recommended on clinical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Doxorubicin 2mg/ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

The applicant's Doxorubicin 2mg/ml Concentrate for Solution for Infusion has been demonstrated to be a generic version of the reference product, Doxorubicin Solution for Infusion (PL 03433/0127, Farmitalia Carlo Erba Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's Doxorubicin 2mg/ml Concentrate for Solution for Infusion and the reference product, Doxorubicin Solution for Infusion (Farmitalia Carlo Erba Limited), are interchangeable. Extensive clinical experience with doxorubicin hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome