Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection

PL 33410/0010 & 0011

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 13
Steps taken after authorisation Page 14
Summary of Product Characteristics Page 15
Product Information Leaflet Page 27
Labelling Page 29
Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection

PL 33410/0010 & 0011

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted APSLA Limited Marketing Authorisations (licences) for the medicinal products Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection (PL 33410/0010-11) on 14th April 2011. These are prescription-only medicines (POM).

Epirubicin 2mg/ml Solution for Injection contains the active substance epirubicin hydrochloride, which is an anti-cancer medicine, belonging to the ‘anthracycline’ drug class. Epirubicin hydrochloride works on cells that are actively growing, to slow down or stop their growth, increasing the likelihood that these cells die. Cells that actively grow, such as cancer cells, are selectively targeted by Epirubicin hydrochloride treatment. This helps to stop the cancer tissue from growing, while normal, healthy tissue is less affected.

Epirubicin hydrochloride is used to treat a variety of cancers, either alone or in combination with other anti-cancer drugs. When injected into the bloodstream, usually by intravenous drip, epirubicin solution can be used to treat:

- Breast cancer
- Ovarian cancer
- Stomach cancer
- Bowel cancer
- Lung cancer
- Cancers of the blood forming tissues, such as - cancer of lymphatic tissue (malignant lymphomas), cancer of the blood, bone marrow or immune system (leukaemias and multiple myeloma)

Epirubicin hydrochloride solution can also be injected into the bladder through a tube:

- to treat pre-cancers and superficial cancers of the bladder wall
- to try and prevent the re-growth of bladder tumours after surgical removal

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection outweigh the risks; hence Marketing Authorisations have been granted.
Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection

PL 33410/0010 & 0011

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 6
Non-clinical assessment Page 9
Clinical assessment Page 10
Overall conclusion and benefit-risk assessment Page 12
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted APSLA Limited Marketing Authorisations for the medicinal products, Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection (PL 33410/0010 and 0011) on 14th April 2011. The products are prescription-only medicines (POM).

These are national applications for Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection, submitted under Article 10(1) of Directive 2001/83 EC, as amended, claiming to be generic versions of the UK reference product, Pharmorubicin Rapid Dissolution (PL 00032/0276), authorised to Pharmacia Ltd (national birth date 14 Dec 1984). The innovator product, Farmarubicine 50 mg freeze-dried powder for injection (Farmitalia Carlo Erba Ltd), was first authorised in France on 1st January 1982. The UK reference product has been authorised for more than 10 years, thus the period of data exclusivity has expired.

Epirubicin hydrochloride is used in the treatment of a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma. Intravesical administration of epirubicin hydrochloride has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

Epirubicin belongs to the pharmacotherapeutic group, anthracyclines and related substances (ATC code - L01D B03). The mechanism of action of epirubicin hydrochloride is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin hydrochloride has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary lung, prostatic and ovarian carcinomas).

The major metabolites of epirubicin hydrochloride that have been identified are epirubicinol (13-OH-epirubicin) and glucuronides of epirubicin and epirubicinol. The 4’-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel to those of the unchanged active substance.

Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution.

The medicinal products are presented as a sterile, freeze-dried, orange-red coloured, lyophilised powder for solution for injection. The products should be dissolved in 5 ml 0.9% sodium chloride or water for injections to get the final concentration of 2 mg/ml. After gentle agitation the reconstituted solution will be transparent and red in appearance. Epirubicin hydrochloride may be further diluted in glucose 5% or sodium
chloride 0.9% and administered as an intravenous infusion (see section 6.6 of the SmPC). This medicine is not for self-administration; it will be administered to the patient by a healthcare professional.

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

The MHRA 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 these products.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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 has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. Routine pharmacovigilance activities according to Volume 9A of the rules governing medicinal products in the EU will be undertaken whilst the product is on the market; this is considered satisfactory. The reference product has been in use for many years and the safety profile of the active is well-established. The excipients used in the medicinal product are well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). Epirubicin hydrochloride is a well-established active substance that has had widespread clinical use for many years. These were applications for generic products, which will not be administered at a higher dosage, for a longer duration or for different indications than were previously authorised. There is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Epirubicin hydrochloride

Nomenclature:

INN: Epirubicin hydrochloride
Chemical name: (8S,10S)-10-[(3-Amino-2,3,6-trideoxy-α-L-arabinopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride

Structure:

Molecular formula: C_{27}H_{29}NO_{11} \cdot HCl
Molecular weight: 580.0 g/mol
CAS No: 56390-09-1
Physical form: An orange-red powder
Solubility: Soluble in water and in methanol, slightly soluble in anhydrous ethanol, practically insoluble in acetone.

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

All aspects of the manufacture and control of epirubicin hydrochloride are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of epirubicin hydrochloride for inclusion in this medicinal product.

The Certificate of Suitability specifies that the retest period of the active substance is 2 years when stored in the proposed commercial packaging.
MEDICINAL PRODUCT

Description & Composition

Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection are presented in 10 ml and 50 ml Type I moulded flint glass vials respectively as a sterile, freeze-dried, orange-red coloured, lyophilised powder for solution for injection. Each 10 ml vial contains 10 mg epirubicin hydrochloride and each 50 ml vial contains 50 mg epirubicin hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely methyl hydroxybenzoate (E218), lactose monohydrate, hydrochloric acid and water for injection. 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 only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to develop generic medicinal products pharmaceutically equivalent to the reference product, Pharmorubicin Rapid Dissolution (PL 00032/0276, Pharmacia Ltd).

A comparison of the physiochemical properties of the test and reference products has been provided. Comparative impurity data were provided for batches of test and reference products and were satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies have been conducted and the results are satisfactory.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. 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 batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
**Container Closure System**

Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection are presented, respectively, in 10 ml and 50 ml Type I moulded flint glass vials with 20 mm bromobutyl rubber stoppers and 20 mm aluminium flip-off tear-off seals. The vials are packaged individually with the Product Information Leaflet (PIL) into cardboard outer cartons. Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been set for the unopened vial, which is satisfactory. Storage instructions are ‘Store below 30°C. Keep the container in the outer carton’.

From a microbiological point of view, the products should be used immediately after reconstitution. For full details of shelf-life and storage conditions for the diluted medicinal products, refer to section 6.3 of the SmPCs. Please also refer to Section 6.6 of the SmPCs for information on proper handling and disposal of the product and contaminated materials.

**Bioequivalence Study**

Bioequivalence studies are not necessary to support these applications for parenteral products.

**Quality Overall Summary**

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 Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user testing report has been evaluated and is accepted. It supports the readability of the package leaflet.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10(1) of Directive 2001/83/EC, as amended, are for Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection, claiming to be generic medicinal versions of Pharmorubicin Rapid Dissolution 10 mg, 20 mg, 50 mg & 150 mg (PL 00032/0276, Pharmacia Ltd).

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of these products from a non-clinical point of view.
CLINICAL ASSESSMENT

INDICATIONS
Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection are used in the treatment of a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma. Intravesical administration of epirubicin hydrochloride has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

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

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY
The toxicology of epirubicin hydrochloride is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
The clinical pharmacology of epirubicin hydrochloride is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

CLINICAL EFFICACY
No new data are submitted and none are required for these types of application. Efficacy is reviewed in the clinical overview. The efficacy of epirubicin hydrochloride is well-established from its extensive use in clinical practice.

Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection are to be administered as an intravenous solution and contain the same active substance, in the same concentration, as the UK reference product, Pharmorubicin Rapid Dissolution (Pharmacia Ltd). Thus, in accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the applicant is not required to submit a bioequivalence study.

CLINICAL SAFETY
No new safety data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of epirubicin hydrochloride is well-known.

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

**Summary of Product Characteristics (SmPC)**

The approved SmPCs are consistent with that for the reference product and are acceptable.

**Patient Information Leaflet (PIL)**

The final PIL is in line with the approved SmPCs and is satisfactory. The PIL user testing has been evaluated and is accepted.

**Labelling**

The labelling is satisfactory.

**CONCLUSION**

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended on medical grounds.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection 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 applications of this type.

CLINICAL
No new data are submitted and none are required for these types of application. Efficacy is reviewed in the clinical overview.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with that for the UK reference product and are satisfactory.

A mock-up PIL has been provided. The PIL is in line with the SmPCs and is satisfactory. 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 (as amended). The results show that the 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.

BENEFIT-RISK ASSESSMENT
The quality of the products 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 Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection and the reference product, Pharmorubicin Rapid Dissolution (Pharmacia Ltd), are interchangeable. Extensive clinical experience with epirubicin hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection

PL 33410/0010 & 0011

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 14th August 2009

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 21st August 2009

3 Following assessment of the applications the MHRA requested further information relating to the quality dossier on 14th January 2010 and 23rd July 2010

4 The applicant responded to the MHRA’s requests, providing further information for the quality sections on 21st June 2010 and 11th January 2011 respectively

5 The applications were granted on 14th April 2011
Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection

PL 33410/0010 & 0011

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection (PL 33410/0010 & 0011) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin Hydrochloride 10 mg powder for solution for injection
Epirubicin Hydrochloride 50 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg / 50 mg of epirubicin hydrochloride
After reconstitution, each vial contains 2 mg/ml epirubicin hydrochloride
Also contains methyl hydroxybenzoate, lactose monohydrate, and hydrochloric acid (for pH adjustment).
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection
A sterile freeze dried orange red coloured lyophilised cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epirubicin hydrochloride has produced responses in a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma.

Intravesical administration of Epirubicin hydrochloride has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

Preparation of the freeze-dried powder
The product should be dissolved in 5 ml 0.9% sodium chloride or water for injections to get the final concentration of 2 mg/ml. The vial contents will be under a negative pressure. To minimize aerosol formation during reconstitution, particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided. After gentle agitation the reconstituted solution will be transparent and red in appearance.

Intravenous administration: Epirubicin hydrochloride is not active when given orally and should not be injected intramuscularly or intrathecally.

It is advisable to give the drug via the tubing of a freely running IV saline infusion after checking that the needle is well placed in the vein. This method minimises the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of Epirubicin hydrochloride from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Conventional doses:

When Epirubicin hydrochloride is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body area; the drug should be injected IV over 3-5 minutes and, depending on the patients’ haematomedullary status, the dose should be repeated at 21 day intervals.
If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

**High doses:**

Epirubicin hydrochloride as a single agent for the treatment of lung cancer at high doses should be administered according to the following regimens:

**Lung cancer**

Small cell lung cancer (previously untreated): 120 mg/m² day 1, every 3 weeks.

Non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m² day 1 or 45 mg/m² days 1, 2, 3, every 3 weeks.

For high dose treatment, epirubicin may be given as an intravenous bolus over 3-5 minutes or as an infusion of up to 30 minutes duration.

**Breast cancer**

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m² (as a single dose on day 1) to 120 mg/m² (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

The drug should be given as an I.V. bolus over 3-5 minutes or as an infusion up to 30 minutes. Lower doses (60-75 mg/ m² for conventional treatment and 105-120 mg/ m² for high dose schedules) are recommended for patients whose bone marrow function has already been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone-marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

The following doses of epirubicin are commonly used in monotherapy and combination chemotherapy for various tumours, as shown:

<table>
<thead>
<tr>
<th>Cancer Indication</th>
<th>Epirubicin Dose (mg/m²)</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced ovarian cancer</td>
<td>60 - 90</td>
<td>50 - 100</td>
<td></td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>60 – 90</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>SCLC</td>
<td>120</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Bladder cancer (carcinoma in situ)</td>
<td>50 mg/50 ml or 80 mg/50 ml weekly for 4 weeks then monthly for 11 months</td>
<td>Prophylaxis: 50 mg/50 ml weekly</td>
<td></td>
</tr>
</tbody>
</table>

*Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals*

When the drug is used in combination with other cytotoxic agents, the doses need to be adequately reduced. Commonly used doses are shown in the table above.

**Impaired liver function**

Since the major route of elimination of Epirubicin hydrochloride is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function based on serum bilirubin levels as follows:

<table>
<thead>
<tr>
<th>Serum Bilirubin</th>
<th>Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 - 51 μmol/l</td>
<td>50%</td>
</tr>
<tr>
<td>&gt; 51 μmol/l</td>
<td>75%</td>
</tr>
</tbody>
</table>
Impaired renal function

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Epirubicin hydrochloride excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine \(> 5 \text{ mg/dL}\).

Intravesical administration:

Epirubicin hydrochloride may be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be used in this way for the treatment of invasive tumours which have penetrated the bladder wall where systemic therapy or surgery is more appropriate (see section 4.3). Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours in order to prevent recurrences.

While many regimens have been used, the following may be helpful as a guide: for therapy 8 x weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg per 50 ml is advised. For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg/50 ml. For prophylaxis, 4 x weekly administrations of 50 mg/50 ml followed by 11 x monthly instillations at the same dosage, is the schedule most commonly used.

**DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS**

<table>
<thead>
<tr>
<th>Dose Epirubicin required</th>
<th>Volume of 2 mg/ml epirubicin injection</th>
<th>Volume of diluent sterile water for injection or 0.9% sterile saline</th>
<th>Total volume for bladder installation</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>15 ml</td>
<td>35 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>50 mg</td>
<td>25 ml</td>
<td>25 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>80 mg</td>
<td>40 ml</td>
<td>10 ml</td>
<td>50 ml</td>
</tr>
</tbody>
</table>

The solution should be retained intravesically for 1 - 2 hours. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void at the end of the instillation time.

4.3 Contraindications

Epirubicin hydrochloride is contraindicated in:

- Patients who have demonstrated hypersensitivity to the active substance or to any of the excipients
- Patients with marked myelosuppression induced by previous treatment with other antitumour agents or by radiotherapy
- Patients treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin.
- Patients with current or previous history of cardiac impairment (including 4th degree muscular heart failure, acute heart attack and previous heart attack which led to 3rd and 4th degree muscular heart failure, acute inflammatory heart diseases, arrhythmia with serious haemodynamic consequences).  
- Patients with acute systemic infections
- Lactation

For intravesical administration, epirubicin is contraindicated in:

- Urinary tract infections
- Invasive tumours penetrating the bladder
• Catheterisation problems
• Vesical inflammation.
• Large volume of residual urine
• Contracted bladder.

4.4 Special warnings and precautions for use

Epirubicin hydrochloride should be administered only under the supervision of qualified physicians experienced in the use of chemotherapeutic agents.

Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

Epirubicin can have genotoxic effects. Therefore, male patients treated with epirubicin are advised not to father a child during and up to six months after treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin.

Women should not become pregnant during treatment with epirubicin. Men and women should use an effective contraception during treatment and for six months thereafter.

Extravasation of epirubicin from the vein during injection may cause severe tissue lesions and necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Careful baseline monitoring of various laboratory parameters and cardiac function should precede initial treatment with epirubicin.

During treatment with epirubicin, red blood cell, white blood cell, neutrophil and platelet counts should be carefully monitored both before and during each cycle of therapy. Leucopenia and neutropenia are usually transient with conventional and high-dose schedules reaching a nadir between the 10th and 14th day; values should return to normal by the 21st day; they are more severe with high dose schedules. Thrombocytopenia (<100,000 platelets/mm³) is experienced in very few patients, even following high doses of epirubicin.

Patients must have adequately recovered from severe stomatitis or mucositis before starting treatment with epirubicin.

In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900-1000 mg/m² should only be exceeded with extreme caution with both conventional and high doses of epirubicin. Above this level the risk of irreversible congestive heart failure increases greatly. An ECG is recommended before and after each treatment cycle. Alterations in the ECG tracing, such as flattening or inversion of the T-wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment. With cumulative doses <900 mg/m², there is evidence that cardiac toxicity rarely occurs. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart failure of the type described for other anthracyclines. In case of cardiac insufficiency, treatment with epirubicin should be discontinued.

Cardiomyopathy induced by anthracyclines, is associated with a persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction. Cardiac monitoring of patients receiving Epirubicin hydrochloride treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques. Electrocardiogram (ECG) changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity. The risk of serious cardiac impairment may be
decreased through regular monitoring of left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The preferred method for repeated assessment of cardiac function is evaluation of LVEF measure by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior to anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict.

As with other cytotoxic agents, Epirubicin hydrochloride may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be carefully checked so that this phenomenon may be recognised and properly managed. Hydration, urine alkalisation and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumour-lysis syndrome.

Heart failure may appear even several weeks after discontinuing, therapy with epirubicin and may be unresponsive to specific medical treatment. The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area and or who are under medical treatment with potentially cardiotoxic medicinal products (see section 4.5).

Before starting therapy with epirubicin and if possible during treatment, liver function should be evaluated (SGOT, SGT, alkaline phosphatase, bilirubin). (see section 4.2).

Epirubicin hydrochloride may impart a red colour to the urine for 1-2 days after administration.

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended that Epirubicin hydrochloride be mixed with other drugs. But Epirubicin hydrochloride can be used in combination with other anticancer drugs.

Drug interactions with epirubicin have been observed with cimetidine, dexteroxapamil, dexrazoxane, docetaxel, interferon α2b, paclitaxel and quinine.

Dexteroxapamil may alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects.

Prior administration of higher doses (900 mg/m² and 1200 mg/m²) of dexrazoxane may increase the systemic clearance of epirubicin and result in a decrease in AUC.

One study found that docetaxel may increase the plasma concentrations of epirubicin metabolites when administered immediately after epirubicin.

The co-administration of interferon α2b may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.

Paclitaxel may affect the pharmacokinetics of epirubicin and its metabolite, epirubicinol. In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin compared with after epirubicin. One study has shown that paclitaxel clearance is reduced by epirubicin.

Quinine may accelerate the initial distribution of epirubicin from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin.

Cimetidine 400 mg b.i.d given prior to epirubicin 100 mg/m² every 3 weeks led to a 50% increase in epirubicin AUC and a 41% increase in epirubicinol AUC (latter <0.05). The AUC of the 7-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity.
Epirubicin used in combination with other cytotoxic agents may result in additive myelotoxicity.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind with a (pre-) treatment with medicines which influence the bone marrow (i.e. cytostatic agents, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivative, antiretroviral agents).

The potential risk of cardiotoxicity may increase in patients who have received concomitant cardiotoxic agents (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), or concomitant (or prior) radiotherapy to the mediastinal area.

If epirubicin is used concomitantly with other medicinal products that may cause heart failure, e.g. calcium channel blockers, then cardiac function must be monitored throughout the course of treatment.

Epirubicin is mainly metabolised in the liver, each concomitant medication which affects hepatic function can also affect the metabolism or the pharmacokinetics of epirubicin and, consequently, its efficacy and/or toxicity.

This product is generally not recommended in combination with live attenuated vaccines.

### 4.6 Pregnancy and lactation

There is no conclusive information as to whether epirubicin may adversely affect human fertility or cause teratogenesis. Experimental data, however, suggest that epirubicin may harm the foetus. Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals. Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus and the possibility of genetic counselling should be considered if they become pregnant during epirubicin therapy. In cancer chemotherapy, epirubicin should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus.

This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding.

### 4.7 Effects on ability to drive and use machines

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

Epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of ability to drive or operate machines.

### 4.8 Undesirable effects

| Frequency | 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) |
|-----------|---------------------|--------------------------|-------------------------------|-----------------------------|---------------------------------------------------------------------------------
<p>| Infections and infestations |                     |                          |                               |                             | Fever, infections, pneumonia, sepsis and septic shock may occur as a result of myelosuppression |
| Neoplasms benign, pneumonia &amp; unspecified (including cysts &amp; polyps) | Secondary acute myeloid leukaemia with or without a pre leukaemic phase in patients treated with epirubicin in combination with DNA – damaging antineoplastic agents. These leukaemia’s have short (1–3 years) latency. |   |
| Blood and the lymphatic system disorders | Myelosuppression* (leucopenia, granulocytopenia (33410/0010 only), neutropenia, febrile neutropenia, thrombocytopenia, anaemia). Haemorrhagia (33410/0010 only) and tissue hypoxia (as a result of myelosuppression) may occur. |   |
| Immune system disorders | allergic reactions following intravesical administration Photosensitivity (33410/0010 only) or hypersensitivity in the case of radiotherapy (“recall phenomenon”) Anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills) |   |
| Metabolism and nutrition disorders | Hyperuricaemia (as a result of rapid lysis of neoplastic cells) |   |
| Cardiac disorders | Cardiotoxicity (ECG changes, tachycardia, arrhythmia, cardiomyopathy, congestive heart failure (dyspnoea, oedema, enlargement of the liver, ascites, pulmonary) |   |</p>
<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th>oedema, pleural effusions, gallop rhythm, ventricular tachycardia, bradycardia, AV block, bundle-branch block (see section 4.4)</th>
<th>Thrombophlebitis</th>
<th>Coincidental cases of thromboembolic events (including pulmonary embolism [in isolated cases with fatal outcome])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting and diarrhoea, which can result in dehydration, loss of appetite and abdominal pain. Oesophagitis and hyperpigmentation of the oral mucosa may also occur.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males</td>
<td>Hot flushes</td>
<td>Hyperpigmentation of skin and nails. Skin reddening.</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td>Amenorrhea, azoospermia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Mucositis may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, mainly along the side of the tongue and the sublingual mucosa. Redness along the infusion vein. Local headache</td>
<td></td>
<td>Fever, chills, dizziness, , hyperpyrexia, malaise, weakness</td>
</tr>
</tbody>
</table>
* High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and have caused adverse events which are no different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm³ for < 7 days) which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

4.9 Overdose

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 days. Treatment should aim to support the patient during this period and should utilise such measures as antibiotics, blood transfusion and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to 6 months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines. Epirubicin is not dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: L01DB03
Pharmacotherapeutic group: anthracyclines and related substances

The mechanism of action of Epirubicin hydrochloride is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin hydrochloride has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after I.V. injection of 60-150 mg/m² of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Between 60-120 mg/m² there is an extensive linear pharmacokinetic, 150 mg/m² is at the
margin of dose linearity. The major metabolites that have been identified are epirubicinol (13-OH-epirubicin) and glucuronides of epirubicin and epirubicinol.

In pharmacokinetic studies of patients with carcinoma in situ of the bladder the plasma levels of epirubicin after intravesical instillation are typically low (<10 ng/ml). A significant systemic resorption can therefore not be assumed. In patients with lesions of the mucosa of the bladder (e.g. tumor, cystitis, operations), a higher resorption rate can be expected.

The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel those of the unchanged active substance.

Epirubicin hydrochloride is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours.

Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The active substance does not cross the blood-brain-barrier.

5.3 Preclinical safety data

The main target organs in rat, rabbit and dog following repeated dosing were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the species tested.

Epirubicin was, like other anthracyclines, mutagenetic, genotoxic, embryotoxic and carcinogenic in rats.

No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic drugs, epirubicin must be considered potentially teratogenic.

A local tolerance study in rats and mice showed extravasation of epirubicin causes tissue necrosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Methyl hydroxybenzoate E218
Lactose monohydrate
Hydrochloric acid
Water for injection

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
Shelf life of the product as packaged for sale: 2 years
Shelf life after reconstitution according to directions:

In-use stability has been demonstrated for 24 hours at 15°C - 25°C and for 48 hours at 2 - 8°C in water for injections and 0.9% w/v sodium chloride solution. However from a microbiological point of view, it is recommended that 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 to 8°C.
6.4 Special precautions for storage
Store below 30°C. Keep the container in the outer carton.
For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container
Epirubicin hydrochloride **10 mg / 50 mg** is produced in **10 ml / 50 ml** Type I moulded flint glass vial with 20 mm bromo butyl rubber stoppers and 20 mm aluminium flip-off tear-off seal.
1 vial per pack

6.6 Special precautions for disposal
Epirubicin hydrochloride may be further diluted in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. For information on the stability of the infusion solutions please refer to section 6.3.

The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

Guidelines for the safe handling and disposal of antineoplastic agents:

1. If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.
2. Preparation of an infusion solution should be performed in a designated aseptic area.
3. Adequate protective disposable gloves, goggles, gown and mask should be worn.
4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 0.9% sodium chloride solution. Then seek medical evaluation by a physician.
5. 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. Always wash hands after removing gloves.
6. 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 detailed below.
7. Pregnant staff should not handle the cytotoxic preparation.
8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0010
PL 33410/0011
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/04/2011

10 DATE OF REVISION OF THE TEXT
14/04/2011
PRODUCT INFORMATION LEAFLET

UKPAR Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection

PL 33410/0010 & 0011

1. WHAT EPIRUBICIN HYDROCHLORIDE IS AND WHAT IT IS USED FOR

Epirubicin Hydrochloride is a medicine used to treat cancer. It is a type of medicine called an anthracycline antibiotic. It is a group of medicines that work by controlling the growth of cancer cells. Epirubicin Hydrochloride can be used in the treatment of cancer of the breast, ovaries, stomach, bowel and lung. In addition, Epirubicin Hydrochloride can be used to treat certain types of blood disorders such as certain types of leukemia and multiple myeloma.

2. BEFORE YOU ARE GIVEN EPIRUBICIN HYDROCHLORIDE

Consider the following information.

- If you are pregnant or planning to become pregnant, you should not use Epirubicin Hydrochloride as it may cause harm to your unborn child.
- If you are breastfeeding, you should not use Epirubicin Hydrochloride as it may cause harm to your baby.
- If you have a history of allergy to Epirubicin Hydrochloride or any other ingredient of this medicine, you should not use it.
- If you have liver or kidney disease, you should use Epirubicin Hydrochloride only under the supervision of a doctor.
- If you have heart disease, you should use Epirubicin Hydrochloride only under the supervision of a doctor.
- If you have low blood pressure, you should use Epirubicin Hydrochloride only under the supervision of a doctor.
- If you have a history of blood disorders, you should use Epirubicin Hydrochloride only under the supervision of a doctor.

3. HOW EPIRUBICIN HYDROCHLORIDE IS GIVEN TO YOU

Epirubicin Hydrochloride is given by injection into a vein or under the skin. The dose is calculated based on your body weight and the type of cancer you have. Your doctor will give you the injection at a hospital or clinic.

4. POSSIBLE SIDE EFFECTS

Epirubicin Hydrochloride may cause side effects in some people. Some of these side effects may be serious and can cause harm to your health. If you experience any of the following side effects, you should contact your doctor immediately:

- Nausea and vomiting
- Diarrhea
- Constipation
- Fatigue
- Rash
- Headache
- Numbness and tingling in your hands and feet
- Blurred vision
- Changes in your hearing or vision

5. HOW TO DEAL WITH SIDE EFFECTS

If you experience any side effects, you should contact your doctor immediately. Your doctor may prescribe medication to help with these symptoms. You should also follow the instructions on your medication labels to minimize the risk of side effects.

6. INFORMED CONSENT

By taking Epirubicin Hydrochloride, you are giving consent to the use of the medicine for your treatment. You understand the risks and benefits associated with the use of Epirubicin Hydrochloride, and you agree to continue with your treatment despite any side effects you may experience.

7. DISCLAIMER

The information provided in this leaflet is intended for educational purposes only and should not be used as a substitute for professional medical advice. Always consult your doctor or other qualified health professional before starting or stopping any medication or treatment.
**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Epirubicin Hydrochloride can cause side effects, although not everybody gets them.

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

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

**Very common (can occur in more than 1 in 10 patients):**
- Fatigue (not normally reversible), reduced growth of hair.

**Common (can occur in more than 1 in 100 patients but less than 1 in 10):**
- Feeling or being sick
- Diarrhoea (which can result in dehydration)
- Loss of appetite
- Abdominal pain
- Inflammation of the gallbladder (cholecystitis)
- High levels of pigments in the mouth
- Hot flushes
- Infection (inflammatory bowel disease) sometimes with blood following administration into the bladder
- Inflammation of muscles in the digestive tract (myositis) including inflammation of the thymus gland (myasthenia)
- Redness along the infusion veins
- Inflammation of veins usually in the legs (locally phlebitis)
- Hardening of the walls of veins (phlebothrombosis)
- Local pain and inner death may occur following accidental injection into the surrounding tissue
- Allergic reactions after being given into the bladder

**Uncommon (can occur in more than 1 in 100 patients, but less than 1 in 10):**
- Darkened urine (hyperpigmentation) of the skin and nails
- Skin rashes
- Inflammation of the blood clot in the veins (thrombophlebitis)
- Sensitivity to light (photosensitivity) or allergic reaction (hyperreactivity) to light therapy – remember to wear sunscreen

**Rare effects (can occur in less than 1 in 1000 patients):**
- Increased transaminase levels (increased levels of some liver enzymes)
- ECG (electrocardiogram) changes
- Rapid heart rate (tachycardia) and ventricular tachycardia
- Slow heart rate (bradycardia)
- Irregular heart beat
- Specific forms of arthritis (AV block and bundle-branch block)
- Heart muscle damage (cardiomyopathy)
- Heart problems (congestive heart disease)
- Difficulty in breathing (dyspnoea)
- Accumulation of fluid (edema) and pulmonary oedema
- Enlargement of the liver
- Accumulation of fluid in the abdominal cavity (ascites)
- Accumulation of fluid between the chest wall and lung (pleural effusion)
- Thickened heart sound (gallop rhythm)
- Bruising (haemorrhages)
- Malignant extension of blood-forming tissues (secondary myelomatous haemorrhage) – mainly seen when given in combination with other antineoplastic medicinal products
- Fever
- Infections
- Diarrhoea
- Abdominal pain
- Severe allergic reactions (anaphylaxis) – with or without shock including skin rash, itching, urticaria, fever and chills
- Abnormal changes in periods (amenorrhoea)
- Lack of levels of male sex hormones (hypogonadism)

Not known (cannot be estimated from the available data):
- Decreased number of white blood cells (granulocytopenia)
- Increased number of blood platelets (thrombocytopenia)
- Nausea accompanied by fever (febrile neutropenia)
- Increased number of red blood cells (erythrocytopenia)
- Decrease in red blood cells (anaemia)
- Blood disorder (haemorrhage)
- Ønset of overt organ failure (organ failure)
- Induction of oxygen supply (tissue hypoxia)
- Fever
- Infections
- Inflammation of the lungs (pneumonitis)
- Acute respiratory insufficiency (ARDS) and severe shock
- Mucosal bleeding of blood vessels by dislodged blood clot (thromboembolic events)

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 nurse.

**4. HOW TO STORE EPIRUBICIN HYDROCHLORIDE**

Keep out of the reach and sight of children.

Do not store Epirubicin Hydrochloride after the expiry date which is stated on the vial label and series after “EXP”. The expiry date refers to the last day of that month. The pharmacist will destroy this medicine when it is prepared for you. If administration is carried out after preparation, the doctor or nurse who is preparing the medicine for you will dispose it off safely.

This aqueous solution should be stored below 30°C in the original container until ready for use.

Reconstitution solution should be used immediately. Medication should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medications no longer required. These measures will help to protect the environment.

**5. FURTHER INFORMATION**

What Epirubicin Hydrochloride contains:
- The active substance is epirubicin hydrochloride.
- The following ingredients are not used: sucrose (sorbitol), methoxypropanediol, hydrochloric acid (pH adjustment) and water for injection.

What Epirubicin Hydrochloride looks like and contents of the package:
- Epirubicin Hydrochloride 10 mg is produced in 1 ml Type I monomer type glass vials with 20 mm rubber stoppers and 20 mm aluminium flip-off tear-off seal.
- Epirubicin Hydrochloride 50 mg is produced in 5 ml Type I moulded flat glass vials with 20 mm rubber stoppers and 20 mm aluminium flip-off tear-off seal.

Each vial contains a single vial

Marketing Authorisation Holder:
- APLISA Limited, Bayside House, 49 North Strand Road, Driblin, I, Ireland
- Manufacturer:
- APZ / Pharmaceuticals & Chemicals (Europe) Limited, 9th floor, C.P. House, 107 Uxbridge Road, Ealing, London, W5 5ST.
- Distributed By:
- APZ / Pharmaceuticals & Chemicals (Europe) Limited, 9th floor, C.P. House, 107 Uxbridge Road, Ealing, London, W5 5ST.
- This leaflet was last revised in October 2019

For any information about this medicine, please contact the local representative of the marketing Authorization Holder:
- APZ / Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 107 Uxbridge Road, Ealing, London W5 5ST.
- Telephone number: 0208 356 3200

**Storing:**

Store the vials at 30°C in the original container until ready for use.

**Usage:**

In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not allow the skin to dry up or wash it vigorously with soap. In case of contact with the eyes, hold back the eyelids of the affected eye(s), and flush with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.

**Always wash hands after removing gloves.**

**Storage:**

Before reconstitution vials should be stored at 30°C in the original container until ready for use. Keep the vials in the outer carton.

**Usage:**

In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not allow the skin to dry up or wash it vigorously with soap. In case of contact with the eyes, hold back the eyelids of the affected eye(s), and flush with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.

**Always wash hands after removing gloves.**

**Storage:**

Before reconstitution vials should be stored at 30°C in the outer carton until ready for use. Keep the vials in the outer carton.

**Usage:**

In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not allow the skin to dry up or wash it vigorously with soap. In case of contact with the eyes, hold back the eyelids of the affected eye(s), and flush with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.

**Always wash hands after removing gloves.**

**Storage:**

Before reconstitution vials should be stored at 30°C in the outer carton until ready for use. Keep the vials in the outer carton.

**Usage:**

In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not allow the skin to dry up or wash it vigorously with soap. In case of contact with the eyes, hold back the eyelids of the affected eye(s), and flush with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.

**Always wash hands after removing gloves.**

**Storage:**

Before reconstitution vials should be stored at 30°C in the outer carton until ready for use. Keep the vials in the outer carton.
UKPAR Epirubicin Hydrochloride 10 mg and 50 mg powder for solution for injection

PL 33410/0010 & 0011

PL 33410/0011

Carton

Epirubicin Hydrochloride 50 mg powder for solution for injection

Epirubicin hydrochloride

CYTOTOXIC AGENT

Single use only.

Discard any unused solution immediately. Dispose of safely in accordance with local cytotoxic protocols.

Powder for solution for injection

50 mg in 50ml vial. Presentation pack: 1 vial

Epirubicin Hydrochloride 50 mg powder for solution for injection

Epirubicin hydrochloride

Each vial contains

50 mg epirubicin hydrochloride

The total contents of the vial when reconstituted as recommended provides 2mg/ml of active substance.

PL Holder:

ASPILA Limited,

Basinina House,

49 North Strand Road,

Dublin 1, Ireland.

Prescribed by:

AFC Pharmaceuticals and

Chemicals (Recepta Ltd.),

Suite 200, Port House,

11 Upho House Road,

Ealing, London, W5 7LG.

Code No. 0693800077

Vial label

Epirubicin Hydrochloride

50 mg powder for solution for injection

50 mg /vial

50 mg epirubicin hydrochloride. The total contents of the vial when reconstituted as recommended provides 2 mg/ml of active substance.

Also contains: Lactose, Methylhydroxypropionate, Hydrochloric acid and Water for injection.

Reconstitute before use.

Read the package leaflet before use.

Store below 30°C.

Storage of diluted product maximum 24 hours at 2 - 8°C. Reconstituted solution should be used immediately.

Single use only. Discard any unused solution immediately. Dispose of safely in accordance with local cytotoxic protocols.

Keep out of the reach and sight of children.

For intravenous/ intravesical use only

PL Holder: ASPILA Limited,

Basinina House, 49 North Strand Road,

Dublin 1, Ireland.

Distributed by:

AFC Pharmaceuticals &

Chemicals (Recepta) Limited,

96 Royal Exchange

Tunisia, Tunisia

Over Printing Area