Epirubicin 2 mg/ml Solution for Injection
(epirubicin hydrochloride)
PL 13621/0034

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Epirubicin 2 mg/ml Solution for Injection
(epirubicin hydrochloride)

PL 13621/0034

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Flynn Pharma Limited a Marketing Authorisation (licence) for the medicinal product Epirubicin 2mg/ml Solution for Injection (PL 13621/0034) on 15th April 2010. This is a prescription-only medicine (POM).

Epirubicin 2mg/ml Solution for Injection contains the active substance epirubicin hydrochloride, which is an anti-cancer medicine. It 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 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

Epirubicin solution 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 affected most by Epirubicin solution treatment. This helps to stop the cancer tissue from growing, while normal, healthy tissue is less affected.

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 Epirubicin 2mg/ml Solution for Injection outweigh the risks; hence a Marketing Authorisation has been granted.
Epirubicin 2 mg/ml Solution for Injection
(epirubicin hydrochloride)

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Flynn Pharma Limited a Marketing Authorisation for the medicinal product Epirubicin 2mg/ml Solution for Injection (PL 13621/0034) on 15th April 2010. The product is a prescription-only medicine (POM).

The application was submitted as a national, abridged application, according to Article 10.1 of Directive 2001/83/EC, as amended. This application is for Epirubicin 2mg/ml Solution for Injection, claiming to be a generic medicinal version of the UK reference product, Pharmorubicin solution for injection 2mg / ml (PL 00032/0275), authorised to Pharmacia Ltd on 15th April 2004. The innovator product, Farmorubicin 2ml/2ml solution for injection (Pfizer Ltd), was first authorised in Denmark and has been authorised in the European Community for more than 10 years, so the period of data exclusivity has expired.

Epirubicin 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 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 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 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 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 unchanged epirubicin.

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 product is presented as a clear, red solution for injection or infusion. The solution may only be diluted with the following solutions for administration as an intravenous solution – sodium chloride 9 mg / ml (0.9%) solution and glucose 50 mg/ml (5%) solution (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 pre-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 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 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 epirubicin. As the application is for a generic version 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. The reference product has been in use for many years and the safety profile of the active is well established.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Epirubicin hydrochloride

Nomenclature:

INN: Epirubicin hydrochloride

Chemical names: \( (8S,10S)-10-[(3-Amino-2,3,6-trideoxy-\alpha-L-arabinohexopyranosyl)oxy]-6,8,11\text{-}\text{tri}hydroxy-8\text{-}(\text{hydroxyacetyl})-1\text{-}methoxy-7,8,9,10\text{-}\text{tetra}hydrotetracene-5,12\text{-}dione \text{hydrochloride} \)

Structure:

![Chemical structure of Epirubicin hydrochloride]

Molecular formula: \( C_{27}H_{29}NO_{11} \), 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 an EDQM Certificate of Suitability. This Certificate is accepted as confirmation of the suitability of epirubicin hydrochloride for inclusion in this medicinal product.
MEDICINAL PRODUCT

Description & Composition
The medicinal product is presented in glass vials of different volumes as a clear, red solution for infusion or injection. Each ml of solution contains 2mg of the active ingredient, epirubicin hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely sodium chloride, sodium lactate solution, water for injections, and hydrochloric acid (for pH adjustment). 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
The impurity profiles were found to be similar for the test and reference products, with all impurities 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 and 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 batch data have been provided for two commercial scale batches of each presentation which indicate that the batches are compliant with the proposed specifications. 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, 10ml, 25ml, or 100ml, closed with chlorobutyl rubber stoppers and aluminium flip-off caps. The vials contain 5ml, 10ml, 25ml, or 100ml of sterile solution of epirubicin 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 10ml, 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 3 years has been set for the unopened vial, which is satisfactory. Storage conditions are ‘Store in a refrigerator (2ºC - 8ºC). Do not freeze. 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

A bioequivalence study is not necessary to support this application for a parenteral product.

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

Conclusion

The proposed product, Epirubicin 2mg/ml Solution for Injection, has been shown to be a generic version of the reference product, Pharmorubicin solution for injection 2mg / ml (PL 00032/0275, Pharmacia Ltd), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the UK reference product. 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.
NON-CLINICAL ASSESSMENT

This abridged application, submitted under Article 10.1 of Directive 2001/83/EC, as amended, is for Epirubicin 2mg/ml Solution for Injection, claiming to be a generic medicinal version of Pharmorubicin solution for injection 2mg / ml (Pharmacia Ltd).

No new pre-clinical data have been supplied with this application and none are required for applications of this type. A pre-clinical overview has been written by a suitably qualified expert and is satisfactory. The CV of the expert has been supplied.
CLINICAL ASSESSMENT

INDICATIONS
Epirubicin 2mg/ml Solution for Injection 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 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 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 epirubicin hydrochloride is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Pharmacodynamics
Epirubicin belongs to the pharmacotherapeutic group, anthracyclines and related substances (ATC code - L01D B03). The mechanism of action of epirubicin 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 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).

Pharmacokinetics
The pharmacokinetics of epirubicin hydrochloride are well described in the product SmPC.

The major metabolites of epirubicin 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 unchanged epirubicin.

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.
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. Epirubicin does not cross the blood-brain-barrier.

**EFFICACY**

No new data are submitted and none are required for this type 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 2mg/ml Solution for Injection is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the UK reference product Pharmorubicin solution for injection 2mg / ml (Pharmacia Ltd). 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.

**SAFETY**

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

**EXPERT REPORT**

The clinical overview contains a sufficient outline of the published literature concerning the clinical pharmacology, efficacy and safety of epirubicin hydrochloride. The report was prepared by an appropriately qualified expert for whom a satisfactory CV has been supplied.

**PRODUCT INFORMATION:**

**Summary of Product Characteristics (SmPC)**

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

**Patient Information Leaflet (PIL)**

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

**Labelling**

The labelling is satisfactory.

**CONCLUSION**

The grounds for establishing the proposed product, Epirubicin 2mg/ml Solution for Injection, as a generic version of the reference product, Pharmorubicin solution for injection 2mg / ml (PL 0032/0275, Pharmacia Ltd), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. When used as indicated, Epirubicin 2mg/ml Solution for Injection has a favourable benefit-to-risk ratio. The grant of a Marketing Authorisation was therefore recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Epirubicin 2mg/ml 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 pre-clinical data were submitted and none are required for an application of this type.

EFFICACY
The applicant’s Epirubicin 2mg/ml Solution for Injection has been demonstrated to be a generic version of the reference product, Pharmorubicin solution for injection 2mg / ml (PL 00032/0275, Pharmacia Ltd).

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.

Colour mock-ups of the labelling have been provided. 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 Epirubicin 2mg/ml Solution for Injection and the reference product, Pharmorubicin solution for injection 2mg / ml (Pharmacia Ltd), are interchangeable. Extensive clinical experience with epirubicin hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
Epirubicin 2 mg/ml Solution for Injection

(epirubicin hydrochloride)

PL 13621/0034

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 20\textsuperscript{th} June 2008

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 26\textsuperscript{th} June 2008

3. Following assessment of the application the MHRA requested further information relating to the quality dossier on 22\textsuperscript{nd} September 2008

4. The applicant responded to the MHRA’s request, providing further information for the quality sections on 21\textsuperscript{st} May 2009

5. The application was determined on 15\textsuperscript{th} April 2010, and granted on 16\textsuperscript{th} April 2010
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Epirubicin 2 mg/ml Solution for Injection is as follows:

1 NAME OF THE MEDICINAL PRODUCT
   Epirubicin 2 mg/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each vial contains 2 mg/ml epirubicin hydrochloride
   5 ml vials contain 10 mg of epirubicin hydrochloride
   10 ml vials contain 20 mg of epirubicin hydrochloride
   25 ml vials contain 50 mg of epirubicin hydrochloride
   100 ml vials contain 200 mg epirubicin hydrochloride
   Epirubicin 2 mg/ml Solution for Injection contains sodium (3.5 mg/ml or 0.15 mmol/ml).
   For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
   Solution for injection or infusion.
   A clear red solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
   Epirubicin 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 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
   Epirubicin is for intravenous or intravesical use only.
   The safety and efficacy of epirubicin in children has not been established.

   Intravenous administration
   Epirubicin 2 mg/ml Solution for Injection is not active when given orally and should not be injected intramuscularly or intracereally.
   It is advisable to administer epirubicin via the tubing of a freely running IV saline infusion after checking that the needle is properly placed in the vein. This method minimises the risk of medicinal product extravasation and makes sure that the vein is flushed with saline after the administration of epirubicin. Extravasation of epirubicin from the vein during injection may give rise to severe tissue lesions, even necrosis. Care should be taken to avoid extravasation (see section 4.4). If extravasation occurs, administration should be stopped immediately. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

   Conventional doses:
   When epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body area. Epirubicin should be administered intravenously over 3-5 minutes. The dose should be repeated at 21 day intervals, depending upon the patient’s haematological status and bone...
marrow function. 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 as a single agent for the treatment of lung cancer at high doses should be administered according to the following regimens:

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 should be given as an I.V. bolus over 3-5 minutes or as an infusion up to 30 minutes.

**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.

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.

**Combination Therapy**

When Epirubicin is used in combination with other antitumour agents, the doses need to be adequately reduced.

**Impaired Liver Function**

The major route of elimination of epirubicin is the hepatobiliary system. The dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. Moderate liver impairment (bilirubin: 1.4-3 mg/100ml) requires a 50% reduction of dose, while severe impairment (bilirubin> 3 mg/100 ml) necessitates a dose reduction of 75%.

**Impaired Renal Function**

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. However, lower starting doses should be considered in patients with severe renal impairment (serum creatinine > 5 mg/dl).

**Intravesical administration**

Epirubicin may be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically 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.

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.

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

Epirubicin is contraindicated in:

- patients who have demonstrated hypersensitivity to the active or any of the excipients
- patients with marked myelosuppression induced by previous treatment with either other anti-neoplastic agents or 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 (see section 4.6).

Contraindications to the intravesical administration of epirubicin are:

- 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 should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for the 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 6 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 (see section 4.6).

Women should not become pregnant during treatment with epirubicin. Men and women should use an effective method of contraception during treatment and for six months thereafter (see section 4.6).

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 in to 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 doses of epirubicin, consideration should be given to

any concomitant therapy with potentially cardiotoxic medicinal products. 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 cardiac failure

increases greatly.

An Electrocardiogram (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 (pre-ejection

period/left ventricular ejection time (PEP/LVET)) and a reduction of the ejection fraction.

Cardiac monitoring of patients receiving epirubicin treatment is highly important and it is

advisable to assess cardiac function by non-invasive techniques.

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 anthracycline or anthracenedione use, the monitoring of cardiac function must be
particularly strict.

Heart failure may appear several weeks after discontinuing treatment 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).

As with other cytotoxic agents, epirubicin 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 minimise potential complications
of tumour-lysis syndrome.

Epirubicin is mainly eliminated via the liver. Before starting therapy with epirubicin, and if
possible during treatment, liver function should be evaluated (serum glutamic oxaloacetic
transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase,
bilirubin). In patients with decreased liver function, epirubicin clearance can be reduced. For
these patients a dose reduction is recommended (see section 4.2).

Serum creatinine levels should be checked regularly prior to and during treatment. For patients
with increased serum creatinine (> 5 mg/dl) a dose reduction is proposed (see section 4.2).

Epirubicin may impart a red colour to the urine for one or two days after administration.

This medicinal product contains 3.5 mg sodium (0.15 mmol) per ml. To be taken into
consideration for patients on a controlled sodium diet.
4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin can be used in combination with other antitumour agents but patients should be monitored for additive toxicity, especially myelotoxicity and gastrointestinal toxicity.

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

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 p< 0.05). The AUC of the 7-deoxydoxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P - 450 activity.

Dexverapamil 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 has been shown to increase plasma concentrations of epirubicin when paclitaxel is administered before epirubicin. When paclitaxel is administered after epirubicin no detectable changes in epirubicin plasma concentrations have been observed. With concomitant use, the latter administration schedule is therefore recommended.

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.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind with a (pre-) treatment with medications which influence the bone marrow (i.e. cytostatic agents, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivate, 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 (see section 5.3). 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 and should use an effective method of contraception during treatment and for six months thereafter.

Male patients treated with epirubicin are advised not to father a child during and up to 6 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 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 (see section 4.4).

Epirubicin has been shown to be excreted into the milk of rats. It is not known whether epirubicin is excreted into human breast milk. Breast-feeding must be discontinued before and during therapy with epirubicin.

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. However, 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

Adverse event frequencies have been categorised as follows: 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)

Cardiac disorders:

Rare: cardiotoxicity (ECG changes, tachycardia, arrhythmia, cardiomyopathy, congestive heart failure (dyspnoea, oedema, enlargement of the liver, ascites, pulmonary oedema, pleural effusions, gallop rhythm), ventricular tachycardia, bradycardia, AV block, bundle-branch block (see section 4.4)).

Blood and the lymphatic system disorders:

Very common: Myelosuppression (leucopenia, granulocytopenia, neutropenia, febrile neutropenia, thrombocytopenia, anaemia).

Very rare, not known: Haemorrhage and tissue hypoxia (as a result of myelosuppression) may occur.

High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and there are no differences to the adverse events 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 a few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

Gastrointestinal disorders:

Common: nausea, vomiting, diarrhoea, which can result in dehydration, loss of appetite and abdominal pain. Oesophagitis and hyperpigmentation of the oral mucosa may also occur.

Skin and subcutaneous tissue disorders:

Very common: alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.

Common: hot flushes

Uncommon: hyperpigmentation of skin and nails. Skin reddening.

Rare: urticaria.

Infections and infestations:

Very common: infections as a result of myelosuppression may occur with fever.

Very rare, not known: pneumonia, sepsis and septic shock may occur as a result of myelosuppression.

Injury, poisoning and procedural complications:

Common: chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration.
Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: secondary acute myeloid leukaemia with or without a pre-leukaemic phase, in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemias have a short (1-3 year) latency.

Vascular disorders:

Uncommon: thrombophlebitis

Coincidental cases of thromboembolic events (including pulmonary embolism [in isolated cases with fatal outcome]) have occurred.

General disorders and administration site conditions:

Common: mucositis – may appear 5 – 10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, ulceration and bleeding, mainly along the side of the tongue and the sublingual mucosa.

Common: redness along the infusion vein. Local phlebitis, phlebosclerosis. Local pain and tissue necrosis (following accidental paravenous injection) may occur.

Uncommon: headache

Rare: fever, chills, dizziness, amenorrhea, azoospermia, hyperuricaemia (as a result of rapid lysis of neoplastic cells). Hyperpyrexia, malaise, weakness and increased transaminase levels have also been reported.

Immune system disorders:

Common: allergic reactions following intravesical administration.

Uncommon: sensitivity to light or hypersensitivity in the case of radiotherapy (“recall phenomenon”).

Rare: anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills).

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 dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code) – L01DB03 Anthracyclines and related substances.

The mechanism of action of epirubicin 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 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 60-150mg/m² of epirubicin 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. The major metabolites 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 those of unchanged epirubicin.

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.

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.

Epirubicin does not cross the blood-brain-barrier.

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. tumour, cystitis, operations), a higher resorption rate can be expected.

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.

It was genotoxic, and, like other anthracyclines, carcinogenic in rats.

Epirubicin was embryotoxic in rats. No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic agents, 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

- Hydrochloric acid (for pH adjustment)
- Sodium lactate solution
- Sodium chloride
- Water for Injections

6.2 Incompatibilities

Prolonged contact with any solution of an alkaline pH (including sodium bicarbonate-containing solutions) should be avoided, as it will result in hydrolysis of the epirubicin. Epirubicin should not be mixed with heparin due to chemical incompatibility, which may lead to precipitation when the medicinal products are in certain proportions.

Epirubicin can be used in combination with other antitumour agents. However it must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 SHELF LIFE

a) Unopened: 3 years

b) Shelf life after first opening the container/dilution according to directions:

After first opening the container, chemical and physical in-use stability has been demonstrated for 72 hours at 2°C to 8°C.
From a microbiological point of view, the product should be used immediately after dilution. 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 conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

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

One colourless glass 5 ml, 10 ml, 25 ml, or 100 ml vial (type I), with chlorobutyl rubber stoppers and aluminium cap with polypropylene cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For methods of administration, see section 4.2.

Preparation instructions

Epirubicin 2 mg/ml Solution for Injection may be further diluted in glucose 5% or sodium chloride 0.9% and administered as an intravenous infusion. The infusion solution should be prepared immediately before use.

The injection solution contains no preservative and any unused portions of the vial should be disposed of immediately in accordance with current requirements.

If any precipitate is observed in the vials before or after dilution, the product should be discarded according to standard procedures for cytotoxic agents.

Guidelines for the safe handling and disposal of antineoplastic agents

As with other potentially toxic compounds, caution should be exercised when handling Epirubicin 2 mg/ml Solution for Injection. The handling of this cytotoxic agent by nursing or medical personnel requires every precaution to guarantee the protection of the handler and his surroundings.

- Pregnant staff should be excluded from working with this medicinal product.
- Personnel should be trained in good techniques for handling cytotoxic preparations.
- Personnel handling epirubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- Preparation of an infusion solution should be performed in a designated aseptic area.
- 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.
- Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In case of contact with the eye(s), hold back the eyelid of the affected eye(s), and flush with copious amounts of water and/or 0.9% sodium chloride solution for at least 15 minutes. Then seek medical evaluation by a physician.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as indicated below.
- Adequate care and precautions should be taken in the disposal of all items (including gloves, syringes, needles, etc.) used in the preparation for administration of the medicinal product or cleaning. Any unused product or waste material should be disposed of in accordance with current requirements.
- Always wash hands after removing gloves.
7 MARKETING AUTHORISATION HOLDER
Flynn Pharma Limited
Alton House
4 Herbert Street
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 13621/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
16/04/2010
PRODUCT INFORMATION LEAFLET

Package Leaflet: Information for the User

**Epirubicin 2 mg/ml Solution for Injection**

epirubicin hydrochloride

The name of your medicine is Epirubicin 2 mg/ml Solution for Injection which will be referred to as Epirubicin Solution throughout this document.

**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 any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. **What Epirubicin Solution is and what it is used for**
2. **Before you use Epirubicin Solution**
3. **How to use Epirubicin Solution**
4. **Possible side effects**
5. **Storing Epirubicin Solution**
6. **Further information**

**1 What Epirubicin Solution is and what it is used for**
Epirubicin Solution contains epirubicin hydrochloride, which is an anti-cancer medicine. It 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 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.

Epirubicin Solution 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 affected most by Epirubicin Solution treatment. This helps to stop the cancer tissue from growing, while normal, healthy tissue is less affected.

**2 Before you use Epirubicin Solution**
Epirubicin Solution should not be used if you:
- are allergic (hypersensitive) to epirubicin hydrochloride or any of the other ingredients in Epirubicin Solution (see list of ingredients in section 6);
- have been treated with other cancer drugs or treated with radiotherapy and are aware that your blood count is low, as Epirubicin Solution can lower it further;
have been treated with other kinds of anthracycline drugs (such as doxorubicin or daunorubicin) in the past, this can increase the risk of side effects on your heart;
- have suffered from heart problems in the past, or are presently receiving treatment for heart problems;
- have a severe infection;
- are breast-feeding.
When administered intravesically (directly into the bladder), Epirubicin Solution should not be used if:
- you have a urinary tract infection;
- the cancer has penetrated the bladder wall;
- your doctor has problems inserting a catheter (tube) into your bladder;
- you have pain or inflammation in your bladder;
- there is a large volume of urine left in your bladder after you empty it;
- your bladder is contracted, meaning you have to urinate frequently.
**Special care will be taken:**
- to ensure the number of cells in your blood does not drop too low. Your doctor will regularly check this;
- if you are experiencing severe inflammation or ulcers in your mouth;
- to check the level of uric acid in your blood. Your doctor will regularly check this;
- if you have problems with your liver or kidney. Your doctor will regularly check your liver and kidney function;
- to ensure your heart is working properly. Your doctor will regularly check this;
- if you have received or are receiving radiotherapy to the chest area;
- if you are sexually active, you are advised to use effective birth control to prevent pregnancy during treatment and for six months afterwards, whether you are male or female.
Please tell your doctor if any of the above apply to you.
Epirubicin Solution is not recommended for use in children.

**Taking other medicines**
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Epirubicin Solution should not be used:
- if you have been treated with high doses of some other anti-cancer medicines, including doxorubicin and daunorubicin which belong to the same group of medicines as epirubicin (called anthracylines). They have similar effects (including their effects on the heart).
Special care will be taken if you are taking any of the following medicines:
- other medicines that may affect your heart such as 5-fluorouracil, cyclophosphamide, cisplatin and taxanes (all used to treat cancer), calcium channel blockers such as diltiazem, amlodipine and nifedipine (used to treat high blood pressure) or radiotherapy to the chest,
- other medicines that may affect your liver,
- cimetidine (used to reduce acidity in your stomach),
- paclitaxel and docetaxel (used for the treatment of some cancers),
- interferon alpha-2b (used for the treatment of some cancers and lymphomas and for some forms of hepatitis),
- quinine (used for the treatment of malaria and for leg cramps),
- dexrazoxane (a medicine sometimes used with doxorubicin),
- dexteroxapam (used to treat some heart conditions),
- medicines that influence the bone marrow, such as other anticancer medicines, sulphonamide and chloramphenicol (both antibiotics), diphenylhydradantoin (used to treat epilepsy), amidopyrine derivatives (anti-inflammatory drugs) and antiretroviral agents (such as acidocey, efavirenz, nevirapine and lamivudine) as they may affect the production of blood cells. This product is generally not recommended in combination with live attenuated vaccines.

**Pregnancy and breast-feeding**

Epirubicin Solution may cause birth defects, so it is important to tell your doctor if you think you are pregnant. It is also important to avoid becoming pregnant while you or your partner are using Epirubicin Solution. Both men and women should use effective contraception during treatment with Epirubicin Solution and for 6 months after treatment has finished. Epirubicin hydrochloride may be harmful to nursing infants. Women must stop breast-feeding before starting treatment with Epirubicin Solution. Ask your doctor or pharmacist for advice before taking any medicine.

**Fertility**

Epirubicin may cause infertility. Therefore, male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

**Driving and using machines**

Epirubicin Solution does not normally cause side effects which affect your ability to drive or use machines. However, you may feel and/or be sick after being given this medicine, therefore, special care should be taken when driving or using machines.

**Important Information about some of the Ingredients of Epirubicin Solution**

This medicine contains 3.5 mg sodium (0.15 mmol) per ml. This should be taken into consideration if you are on a controlled sodium diet.

**3 How to use Epirubicin Solution**

Epirubicin Solution should only be given to you by doctors or nurses experienced in giving chemotherapy.

Epirubicin Solution will be given to you either as an injection or drip (infusion) into a vein or as an injection into the bladder through a tube (catheter). Your doctor will decide the right amount to use (the dose), depending on the type of cancer you have, your health and your body surface area (calculated from your height and weight).

**Injection or infusion into a vein**

The medicine may be given as an injection into a vein over 3–5 minutes. It may also be diluted with glucose (sugar solution) or sodium chloride (salt water) before it is infused slowly, usually via a drip into a vein over 30 minutes. You may be given another dose of this medicine in 3 weeks, although the dose could be reduced or postponed depending on your blood count.
The usual dose is 60-90 mg/m² body area, injected into the vein over 3–5 minutes. Higher doses may be used for lung cancer and breast cancer, as follows:
- for small cell lung cancer, 120 mg/m² body area every 3 weeks,
- for non-small cell lung cancer, 135 mg/m² body area (which may be divided into 3 doses) every 3 weeks,
- for breast cancer, 100–120 mg/m² body area (which may be divided into 2 doses) every 3–4 weeks. You will probably also be given other medicines to help treat your breast cancer.

Your dose may be reduced if you have liver and/or kidney problems; or your bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age or by cancer.

Injection into the bladder through a tube ['catheter'] (intravesical administration)

The medicine may be given directly into the bladder using a catheter. The dose and number of days’ treatment depend on the type of bladder cancer you have, your condition and any other treatment you receive. If this route is used, you should not drink any fluids for 12 hours before treatment so that your urine will not dilute the medicine too much. The solution should be kept in your bladder for 1–2 hours after treatment. You will be rotated occasionally to ensure even exposure of all parts of the bladder to the medicine.

Care should be taken to ensure that the contents of the bladder, when emptied do not come into contact with the skin. In case of skin contact, thoroughly wash the affected area with soap and water but do not scrub.

While you are receiving epirubicin your doctor will give you regular blood tests. This is to measure the effect the medicine is having. Your doctor will also carry out regular tests on how your heart is working.

If you receive more Epirubicin Solution than you should
As this medicine will be given to you whilst you are in hospital, it is unlikely that you will be given too little or too much. Tell your doctor if you have any concerns.

4 Possible side effects

Like all medicines Epirubicin Solution can cause side effects, although not everybody gets them. If you experience any of the following while under treatment with Epirubicin Solution you must tell your doctor immediately:
- if there is any redness, pain or swelling at the injection site;
- if you have symptoms of heart problems, such as chest pain, shortness of breath, swelling of your ankles (these effects may occur up to several weeks after finishing treatment with epirubicin);
- if you have a severe allergic reaction, symptoms include faintness, skin rash, itching, swelling of the face, difficulty in breathing or wheezing. In some cases collapse may occur. These are very serious side effects. You may need urgent medical attention.

If you experience any of the following tell your doctor as soon as possible:

Very common side effects (more than 1 in 10 patients):
- loss of hair, which is normally reversible and accompanied by lack of beard growth in males,
- decrease in white blood cell count which may make you more susceptible to infections,
- decrease in red blood cell count which may make you feel tired and weak and look pale,
- decrease in platelet count which may make you bruise or bleed more easily.

**Common side effects**
(more than 1 in 100 patients):
- nausea (feeling sick)
- vomiting (being sick)
- diarrhoea which may make you dehydrated
- loss of appetite
- abdominal pain
- heartburn, caused by inflammation of the oesophagus
- dark areas (pigmentation) in your mouth
- swelling and/or pain and/or bleeding in your digestive tract including the mouth, mainly along the side and underside of your tongue
- hot flushes
- redness, swelling and/or hardening of the vein into which Epirubicin Solution is injected

- if Epirubicin Solution is accidentally injected outside the vein, pain and tissue destruction at the injection site
- after injection into the bladder, allergic reactions or bladder inflammation causing pain on passing urine, a change in frequency of passing urine and possibly blood in your urine.

**Uncommon side effects**
(less than 1 in 100 patients):
- sensitivity to light
- acute radiation reactions such as skin inflammation ('recall phenomenon') in areas that have been treated with radiotherapy in the past
- thrombophlebitis (inflammation of the vein caused by a blood clot)
- dark areas (pigmentation) of the skin and nails
- skin reddening
- headache.

**Rare side effects**
(less than 1 in 1000 patients):
- severe allergic reactions (anaphylactic/anaphylactoid reactions) with or without shock including skin rash, pruritis (itching), fever and chills
- heart problems (changes in the heart rhythm or heart failure)
- urticaria (nettle rash)
- fever
- chills
- dizziness
- absence of menstrual periods
- reduced or absent sperm in the semen
- high levels of uric acid in the blood (indicator of cell destruction)
- secondary leukaemia (cancer of the blood) has developed in some patients who have been given epirubicin in combination with other anti-cancer medicines
- exceptionally high fever
- generally feeling unwell
- weakness
- increased levels of liver enzymes (indicator of liver damage).

**Very rare side effects**
(less than 1 in 10,000, not known [cannot be estimated from the available data]):
- embolism (blockage of a blood vessel) including pulmonary embolism (blood clot in the lungs)
- pneumonia (chest infection)
UKPAR Epirubicin 2 mg/ml Solution for Injection

■ symptoms of an infection due to the lack of white blood cells
■ decrease in blood cell count that may lead to bleeding and/or shortage of oxygen in the tissue.
Your urine may be red for a couple of days after being given epirubicin.
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.

5 Storing Epirubicin Solution
Keep out of the reach and sight of children.
Store in a refrigerator (2° - 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Epirubicin Solution should not be used after the expiry date which is stated on the vial label and outer carton.
Your doctor should use the Epirubicin Solution as soon as it has been made, or within 24 hours if stored in a refrigerator (2° - 8°C).
If the Epirubicin Solution goes cloudy after preparation, your healthcare professional will dispose of it safely.
Your healthcare professional will dispose of any used vials according to hospital standard procedures applicable to cytotoxic medicines.

6 Further information
What Epirubicin Solution contains
■ The active substance is epirubicin hydrochloride 10 mg, 20 mg, 50 mg or 200 mg.
■ The other ingredients are hydrochloric acid, sodium lactate solution, sodium chloride and water for injections.

What Epirubicin Solution looks like and contents of the pack
Epirubicin Solution is a solution for injection or infusion.
Epirubicin Solution is a clear red liquid. It comes in a carton containing one colourless glass, rubber stoppered vial. The vial contains 5 ml, 10 ml, 25 ml or 100 ml of Epirubicin Solution.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation Holder is:
Flynn Pharma Limited
Alton House
4 Herbert Street
Dublin 2
Ireland
The Manufacturer is:
Canernova GmbH
Onkologische Arzneimittel
Hirtenweg 2-4
79276, Reute
Germany

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Flynn Pharma LTD
INFORMATION FOR HEALTHCARE PROFESSIONALS

Epirubicin 2 mg/ml Solution for Injection
epirubicin hydrochloride

The following information is intended for medical or healthcare professionals only:
Epirubicin is for intravenous or intravesical use only.

Incompatibilities
Prolonged contact with any solution of an alkaline pH (including sodium bicarbonate-containing solutions) should be avoided, as it will result in hydrolysis of the epirubicin. Epirubicin should not be mixed with heparin due to chemical incompatibility, which may lead to precipitation when the medicinal products are in certain proportions.
Epirubicin can be used in combination with other antitumour agents. However this medicinal product must not be mixed with other medicinal products except those mentioned in the dilution instructions below.

Preparation Instructions
Epirubicin 2 mg/ml Solution for Injection may be further diluted in glucose 5% or sodium chloride 0.9% and administered as an intravenous infusion. The infusion solution should be prepared immediately before use.
The injection solution contains no preservative and any unused portions of the vial should be disposed of immediately in accordance with current requirements.

If any precipitate is observed in the vials before or after dilution, the product should be discarded according to standard procedures for cytotoxic agents.

Methods of Administration

Intravenous administration
For conventional dosing, Epirubicin should be given as an I.V. bolus over 3-5 minutes. For high dose treatment, it may alternatively be given as an infusion for up to 30 minutes.
Epirubicin is not active when given orally and should not be injected intramuscularly or intrathecally.
It is advisable to administer epirubicin via the tubing of a freely running IV saline infusion after checking that the needle is properly placed in the vein. This method minimises the risk of medicinal product extravasation and makes sure that the vein is flushed with saline after the administration of epirubicin. Extravasation of epirubicin from the vein during injection may give rise to severe tissue lesions, even necrosis. Care should be taken to avoid extravasation. If extravasation occurs, administration should be stopped immediately.
Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Intravesical administration
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 instillation, the patient should be rotated occasionally to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. The patient should be instructed to void at the end of the instillation time.
Guidelines for the safe handling and disposal of antineoplastic agents

As with other potentially toxic compounds, caution should be exercised when handling Epirubicin 2 mg/ml Solution for Injection. The handling of this cytotoxic agent by nursing or medical personnel requires every precaution to guarantee the protection of the handler and his surroundings.

- Pregnant staff should be excluded from working with this medicinal product.
- Personnel should be trained in good techniques for handling cytotoxic preparations.
- Personnel handling epirubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- Preparation of an infusion solution should be performed in a designated aseptic area.
- 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.
- Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In case of contact with the eye(s), hold back the eyelid of the affected eye(s), and flush with copious amounts of water and/or 0.9% sodium chloride solution for at least 15 minutes. Then seek medical evaluation by a physician.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as indicated below.
- Adequate care and precautions should be taken in the disposal of all items (including gloves, syringes, needles, etc.) used in the preparation for administration of the medicinal product or cleaning. Any unused product or waste material should be disposed of in accordance with current requirements.
- Always wash hands after removing gloves.

Storage

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

After first opening the container, chemical and physical in-use stability has been demonstrated for 72 hours at 2°C to 8°C.
From a microbiological point of view, the product should be used immediately after dilution. 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 conditions.
UKPAR Epirubicin 2 mg/ml Solution for Injection  
PL 13621/0034

LABELLING

Carton – 10 mg in 5 ml vial
UKPAR Epirubicin 2 mg/ml Solution for Injection PL 13621/0034

Carton – 200mg in 100ml vial