

Epirubicin 10mg/vial for injection
Epirubicin 50mg/vial for injection

Epirubicin Hydrochloride

PL 21040/0001

PL 21040/0002

Sindan S.A.R.L.

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Lay Summary

Epirubicin is an anti-cancer drug related to the anthracycline antibiotic drugs. It has produced responses in a wide range of different cancers, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphoma, leukaemias and multiple myelomas. Intravesical administration of epirubicin has been found to be beneficial in the treatment of superficial bladder carcinoma, carcinoma-in-situ and the prophylaxis of recurrences after transurethral resection. Epirubicin is toxic to cells but the precise nature of its anti-cancer actions remains to be determined.

The Market authorisation holder Sindan S.A.R.L. was granted a product licence for these generic products on the basis of essential similarity with the originator product. The original product is listed as Farmarubicine 10mg freeze-dried powder for injection licensed in France in 1982 to Lab. Farmitalia Carlo Erba. The reference product is listed as Pharmorubicin RD 10mg powder for injection licensed to Farmitalia Carlo Erba Ltd UK under licence PL 03433/0082 granted on the 14th December 1984.

The assessors considered that there was a positive risk/benefit for these products and a Marketing Authorisation was granted on 18th January 2006.

Scientific Discussion

Pharmaceutical Assessment

1. INTRODUCTION

This Public Assessment Report is based on the Assessment Report generated in response to applications for Marketing Authorisation in the UK for Epirubicin for Injection 10mg/vial (PL 21040/001) and Epirubicin for Injection 50mg/vial (PL 21040/0002). These were submitted under Article 10.1(a) (iii) of Directive 2001/83 (as amended), first paragraph so called generic application.

Marketing Authorisations for these products were granted on 18th January 2006.

The original product is listed as Farmarubicine 10mg freeze-dried powder for injection licensed in France in 1982 to Lab. Farmitalia Carlo Erba. The reference product is listed as Pharmorubicin RD 10mg powder for injection licensed to Farmitalia Carlo Erba Ltd UK under licence PL 03433/0082 granted on the 14th December 1984. The RD product is a rapid dissolution version of the original product.

Though PL 03433/0082 was an existing licence when this application was submitted, it has since been cancelled (14th November 2004). The current UK product is PL 00032/0276 which is listed as a medically targeted application, granted to Pharmacia on the 14th May 2004.

2. DRUG SUBSTANCE

2.1 General information

The manufacturer of the drug substance, epirubicin hydrochloride, has provided a Certificate of Suitability.

2.2 Impurities

Satisfactory specifications and processes for the identification and measurement of impurities and residual solvents were provided. Testing of the drug substance demonstrated that impurities and residual solvents were within the specified limits.

2.3 Control of drug substance

2.3.1 Specification

The active substance manufacturer specification was provided for epirubicin hydrochloride. The specification is in compliance with the requirements of the European Pharmacopoeia and the certificate of suitability.

Tests for appearance, solubility, identification and detection of impurities are carried out by both active substance manufacturer and finished product manufacturer and are in compliance with requirements of the European Pharmacopoeia. No validation data has been presented on the basis that the methods are pharmacopoeia methods.

2.3.2 Container closure system

The active substance is packaged in 2-ply polyethylene bag and heat sealed and then placed inside an aluminium tin. The tins are placed in a carton, the inner wall of which has foamed plastic adherent. The gap between the foamed plastic and aluminium tin is filled with dry ice and all sealed cartons are stored at 2°C to 8°C. The packaging size is 1kg/tin. Relevant details on specifications and routine tests on the packaging material have been provided.

2.3.3 Stability

Stability data has been presented for 3 batches. These batches are not production scale but are at least 10% of the final production batch size. The batches have been stored for 36 months under standard conditions. The products have been tested to the release specification. The three batches at 2°C-8°C remain in specification throughout the 36 month study. The applicant has proposed a 2 year expiration period when stored between 2°C and 8 °C, which is considered acceptable.

3. DRUG PRODUCT

3.1 Composition

The qualitative composition of the products are:

Epirubicin 10mg/vial; epirubicin hydrochloride 10mg, methylparahydroxybenzoate, lactose monohydrate.

Epirubicin 50mg/vial; epirubicin hydrochloride 50mg, methylparahydroxybenzoate, lactose monohydrate.

The products are powders for solution for injection. The products are packed in colourless type I glass vials with a filling capacity of 8ml and 50ml respectively for the two strengths. The vials have a bromobutyl rubber stopper with a metal cap.

3.2 Pharmaceutical Development

3.2.1 Formulation development

Compatibility of epirubicin hydrochloride and the excipients has not been shown as the product uses the same qualitative composition as the reference product, as stated in the SPC. Compatibility has also been indirectly demonstrated by the stability results.

The development program focuses on the production of a product being essentially similar to the reference product based on the data available in the literature. The formulas of the two strengths (10mg and 50mg) can be considered the same as the ratios between the components are the same.

3.3 Manufacture

3.3.1 Manufacturer(s)

A satisfactory manufacturing permit covering GMP has been supplied by the manufacturers.

3.3.2 Batch formula

Satisfactory batch data was provided.

3.3.3 Manufacturing process and process controls

An acceptable description of the manufacturing process and process controls was provided along with the necessary validation data.

3.4 Control of excipients

3.4.1 Specification

Methyl parahydroxybenzoate, lactose monohydrate, water for injections and nitrogen have monographs in the European Pharmacopoeia.

Relevant sampling details, specifications and quality reports have been provided from the finished product manufacturer for the excipients. Certificates of analysis have been provided from the finished product manufacturer for all the products.

The analytical methods used to test the excipients are those provided in the European Pharmacopoeia.

Relevant statements and certification on TSE/BSE for lactose have been provided.

3.5 Control of drug product

3.5.1 Specification

The finished product specifications for both strengths of the product were provided and are acceptable. Validation data has been provided for measurement of excipients and impurities and are acceptable.

3.5.2 Reference standards

Suitable information on the reference standards has been provided.

3.6 Container closure system

Relevant specifications and quality reports have been supplied from the finished product manufacturer. Certificates of quality and drawings from the packaging manufacturer have also been supplied.

Certification of compliance to the EU directives (89/109/EEC) on contact materials for the glass vials has been provided.

3.7 Stability

Stability has been conducted on production scale batches of the 10mg and 50mg strengths. In all cases the container closure system is that proposed for commercial use.

The applicant is proposing a shelf life of 36 months with precautions for storage 'to be stored in the original package' due to known sensitivity to light exposure. The applicant is proposing a shelf life of 24 hours at 25°C protected from light and 48 hours at 2°C-8°C for the reconstituted solutions. This is acceptable.

Confirmation has been provided that as well as completion of the existing studies, one batch per year will be placed on stability as a continuous stability program. The stability of the reconstituted solution will also be included. The post approval stability commitment will include vials in the upright and inverted positions. Photostability data has been presented in-line with the guidelines. The applicant has proposed storage instructions of store in the original package which on the basis of the data provided is more than acceptable.

3.8 Other Information

3.8.1 Biostudy

The clinical work has been presented bibliographically.

3.8.2 Essential similarity

Comparable impurity profiles and levels have been demonstrated for one batch of both strengths of Epirubicin with one batch of both strengths of Pharmorubicin. Additionally the dissolution of the powder has been compared for batches of both strengths. The data presented would show reasonable comparability.

4. PRODUCT LITERATURE

4.1 SPC

The SPC has been completed in-line with the quality section and SPC guideline and is acceptable.

4.2 PIL

The PIL has been completed in-line with the SPC and guidelines and is acceptable.

4.3 LABEL

The label has been completed in-line with the SPC and guidelines and is acceptable.

5. ADMINISTRATIVE

5.1 MAA form

The MAA has been completed in-line with the SPC and guidelines and is acceptable.

5.2 Quality Overall Summary

A quality overall summary was provided.

6. CONCLUSIONS

A marketing authorisation was granted for Epirubicin for Injection 10mg/vial and Epirubicin for Injection 50mg/vial.

Pre-clinical Assessment

No new pre-clinical data were submitted which is acceptable for this type of application.

Medical Assessment

1. INTRODUCTION AND BACKGROUND

This Public Assessment Report is based on the Assessment Reports for two national, abridged applications for two epirubicin hydrochloride products, Epirubicin 10mg Powder (PL 21040/0001) for Injection and Epirubicin 50mg Powder for Injection (PL 21040/0002) for the treatment of a range of neoplastic conditions by the intravenous and intravesical routes. Marketing Authorisations were granted on the 18th January 2006.

The applicant claims essential similarity to Pharmorubicin, 2mg/ml, Solution for Injection (PL 03433/0135) marketed by Pharmacia that has been licensed in the EU for more than 10 years (1985) and is currently licensed in the UK. The drug is well established for use in the requested indications.

2. INDICATIONS

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

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

3. POSOLOGY AND METHOD OF ADMINISTRATION

Intravenous administration

Epirubicin is not active when given orally and should not be administered as intrathecal or intramuscular injection.

It is advisable to give the drug via the tubing of a freely - running intravenous infusion of isotonic sodium saline, after checking that the needle is well placed in the vein. The 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 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 is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body area; the drug should be injected intravenous over 3-5 minutes and depending on the patient's haematomedullary status, the dose should be repeated at 21 days intervals.

Dose modification (reduction) following signs of toxicity (specifically severe neutropenia /neutropenic fever and thrombocytopenia, which could persist on Day 21 after the first dose) could be required or the following dose could be delayed, as the case of liver impairment.

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 day 1, 2, 3 every 3 weeks.

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 doses 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.

In patients with hepatic impairment, the dose should be adjusted according to bilirubin plasma levels. The total dose may be administered in divided doses over 2-3 days.

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

Since the major route of elimination of epirubicin is the hepato-biliary system, the doses should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. For bilirubin levels within 1.4-3 mg/dl the dose should be reduced by 50%, and for levels higher than 3 mg/dl by 75%.

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route.

Intravesical administration

Epirubicin may be given by intravesical administration for the treatment of superficial bladder carcinoma 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.

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/ 50 ml is advised. For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased to 80 mg/50 ml followed by 11x monthly instillations at the same dosage, is the schedule most commonly used.

The solution should be retained intravesically 1 hour. 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. CLINICAL PHARMACOLOGY

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

5. EFFICACY

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

6. SAFETY

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

7. OVERVIEWS

Non-clinical and clinical overviews were provided.

8. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC was amended to be as near to identical as possible with the cross-referenced Pharmorubicin SPC.

9 PATIENT INFORMATION LEAFLET

A number of changes to the patient information leaflet were requested. These were to help explain the indication and to further clarify the contraindications and the potential adverse effects for these products.

10 LABELLING

A number of changes to the labelling of this product were requested and the final labels are acceptable..

11 TECHNICAL LEAFLET

A technical leaflet was requested for use by staff administering these epirubicin products and a satisfactory leaflet was supplied by the company.

12. APPLICATION FORM (MAA)

The MAA is medically satisfactory.

13. DISCUSSION

The absence of clinical data is satisfactory. Minor changes to the product literature were required.

14 MEDICAL CONCLUSION

After resolution of the outstanding points, a marketing authorisation was granted for these preparations.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The quality characteristics of Epirubicin 10mg/vial and Epirubicin 50mg/vial 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No new efficacy data were submitted and none are required for this type of application.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and the product is essentially similar to the reference product the product has a positive risk/benefit assessment.

Steps Taken During Assessment

1	The MHRA received the marketing authorisation applications on 18 th March 2004.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 6 th May 2004.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 19 th January 2005 and further information relating to the quality dossiers on 9 th March 2005 and 5 th July 2005.
4	The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 14 th February 2005 additional information on the quality dossier was received on the 10 th October 2005 and 26 th October 2005.
5	The applications were determined on 18 th January 2006.

Summary of Product Characteristics

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCTS

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection
Epirubicin Hydrochloride 50 mg Powder for Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 8 ml vial contains epirubicin hydrochloride 10 mg.
One 50 ml vial contains epirubicin hydrochloride 50 mg.

After reconstitution with 5/25 ml sodium chloride/ water for injections, each vial contains 2 mg/ml epirubicin hydrochloride

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.
Red-orange, freeze-dried, sterile, powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Epirubicin Hydrochloride Powder for Solution for Injection has produced responses in a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemia and multiple myeloma.

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

4.2. Posology and method of administration

Epirubicin Hydrochloride Powder for Solution for Injection is not active when given orally and is not for intrathecal or intramuscular injection. The freeze-dried powder may be reconstituted with 0.9 % sodium chloride for injection or water for injections. For further information see section 6.6.

Intravenous use

It is advisable to give the drug via the tubing of a freely running intravenous infusion (0.9% sodium chloride injection), 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 (0.9% sodium chloride injection) after the administration of the drug. Extravasation of Epirubicin Hydrochloride Powder for Solution for Injection 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.

Discard any unused solution.

Conventional doses

When Epirubicin Hydrochloride Powder for Solution for Injection is used as a single agent, the recommended dose in adults is 60-90 mg/m² body area; the drug should be injected intravenously over 3-5 minutes and, depending on the patient's haematomedullary status, the dose should be repeated at 21 days intervals.

High doses

Epirubicin Hydrochloride Powder for Solution for Injection 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 day 1, 2, 3 every 3 weeks.

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 dose 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.

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

Since the major route of elimination of epirubicin is the hepato-biliary system, the doses 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%. Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route.

Intravesical use

Epirubicin may be given by intravesical administration for the treatment of superficial bladder carcinoma 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. 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 0.9% sodium chloride injection or water for injections). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/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 11x monthly instillations at the same dosage, is the schedule most commonly used.

For the preparation of the solution for intravesical use see section 6.6.

The solution should be retained intravesically for 1 hour. 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 Powder for Solution for Injection is contraindicated in patients with marked myelosuppression induced by previous treatment with other antitumour agents or by radiotherapy and in patients already treated with maximal cumulative doses of other anthracyclines such as Doxorubicin or Daunorubicin.

The drug is contraindicated in patients with current or previous history of cardiac impairment.

4.4. Special warnings and precautions for use

Epirubicin therapy should be administered only under the supervision of a qualified physician experienced in antineoplastic and cytotoxic therapy. Treatment with high dose Epirubicin Hydrochloride Powder for Solution for Injection in particular requires the availability of facilities for the care of possible clinical complications due to myelosuppression.

Initial treatment calls for a careful baseline monitoring of various laboratory parameters and cardiac function.

During each cycle of treatment with Epirubicin Hydrochloride Powder for Solution for Injection, patients must be carefully and frequently monitored. Red and white blood cells, neutrophils and platelet counts should be carefully assessed both before and during each cycle of therapy. Leukopenia and neutropenia are usually transient with conventional and high-dose schedules, reaching a nadir between the 10th and 14th day and returning to normal values by the 21st day; they are more severe with high dose schedules. Very few patients, even receiving high doses, experience thrombocytopenia (<100,000 platelets/mm³).

Before starting therapy and if possible during treatment, liver function should be evaluated (SGOT, SGPT, alkaline phosphatase, bilirubin). A cumulative dose of 900-1000 mg/m² should only be exceeded with extreme caution with both conventional and high doses.

Above this level the risk of irreversible congestive cardiac failure increases greatly. There is objective evidence that cardiac toxicity may occur rarely below this range. However, cardiac function must be carefully monitored during treatment to minimise the risk of cardiac failure of the type described for other anthracyclines.

Heart failure can appear even several weeks after discontinuing treatment and may prove 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.

In establishing the maximal cumulative doses of Epirubicin Hydrochloride Powder for Solution for Injection, any concomitant therapy with potential cardiotoxic drugs should be taken into account.

It is recommended that an ECG before and after each treatment cycle should be carried out. 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.

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 Powder for Solution for Injection treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques such as ECG, echocardiography and, if necessary, measurement of ejection fraction by radionuclide angiography.

Like other cytotoxic agents, Epirubicin Hydrochloride Powder for Solution for Injection 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 controlled pharmacologically.

Epirubicin Hydrochloride Powder for Solution for Injection may impart a red colour to the urine for 1-2 days after administration.

4.5. Interactions with other medicinal products and other forms of interaction

It is not recommended that Epirubicin Hydrochloride Powder for Solution for Injection be mixed with other drugs. But Epirubicin Hydrochloride Powder for Solution for Injection can be used in combination with other anticancer drugs.

Cimetidine increases the formation of the active metabolite of epirubicin and the exposure of the unchanged epirubicin by pharmacokinetic interaction.

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. This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding. Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Apart from myelosuppression and cardiotoxicity, the following adverse reactions may occur:

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

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.

Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea.
Hyperpyrexia.

Fever, chills and urticaria have been rarely reported; anaphylaxis may occur.

High doses of epirubicin have been safely administered in a large number of

untreated patients having various solid tumours and has caused adverse events which are not 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 a few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

During intravesical administration, as drug absorption is minimal, systemic side effects are rare; more frequently chemical cystitis, sometimes haemorrhagic, has been observed.

Haematological:

The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with epirubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 year) latency period.

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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: cytotoxic antibiotics and related substances, anthracyclines. 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 leukemias, 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. 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 constantly lower and virtually parallel those of the unchanged drug.

Epirubicin Hydrochloride Powder for Solution for Injection 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 drug does not cross the blood-brain-barrier. When epirubicin is administered intravesically the systemic absorption is minimal.

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 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

Lactose (monohydrate), methyl parahydroxybenzoate.

6.2. Incompatibilities

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. Epirubicin Hydrochloride Powder for Solution for Injection should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.

Epirubicin Hydrochloride Powder for Solution for Injection can be used in combination with other antitumour agents, but it is not recommended that it be mixed with other drugs.

6.3. Shelf life

Shelf life of the product as packaged for sale

3 years

Shelf life after reconstitution according to directions:

Chemical and physical in-use stability has been demonstrated for 28 hours at $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$, $60\text{ } \% \text{ RH} \pm 5\text{ } \% \text{ RH}$ and for 52 hours at $2\text{-}8^{\circ}\text{C}$. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at $2\text{ - }8\text{ }^{\circ}\text{C}$, unless reconstitution has taken place in controlled and validated conditions.

6.4. Special precautions for storage

Store in the original package.

6.5. Nature and contents of container

Carton box with 1 colourless type I glass vial (filling capacity 8 ml, 50 ml respectively) closed with bromobuthyl rubber and aluminium-plastic Flip-Top cap.

6.6. Instruction for use, handling and disposal

Preparation of the freeze-dried powder for intravenous use. The product should be dissolved in 5 ml or 25 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 use

Epirubicin should be administered into the tubing of a freely flowing infusion (0.9% sodium chloride). To minimize the risk of thrombosis or perivenous extravasation, the usual infusion times range between 3 and 20 minutes depending upon dosage and volume of the infusion solution. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see Warning and Precautions).

Intravesical use

The product should be dissolved in 5 ml or 25 ml 0.9% sodium chloride injection or water for injections to get the final concentration of 2 mg/ ml.

Epirubicin should be instilled using a catheter and retained intravesically for 1 hour. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation.

The following protective recommendations are given due to the toxic nature of this substance:

Personnel should be trained in good technique for reconstitution and handling.

- Pregnant staff should be excluded from working with this drug.
- Personnel handling Epirubicin Hydrochloride Powder for Solution for Injection should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning including gloves, should be placed in high-risk, waste disposal bags for high temperature incineration. Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. In case of contact with the eye(s), hold back the eyelid 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.

7. MARKETING AUTHORISATION HOLDER

SINDAN S.à.r.l
16, Allée Marconi
L- 2112 Luxembourg

8. MARKETING AUTHORISATION NUMBERS

PL 21040/0001

PL 21040/0002

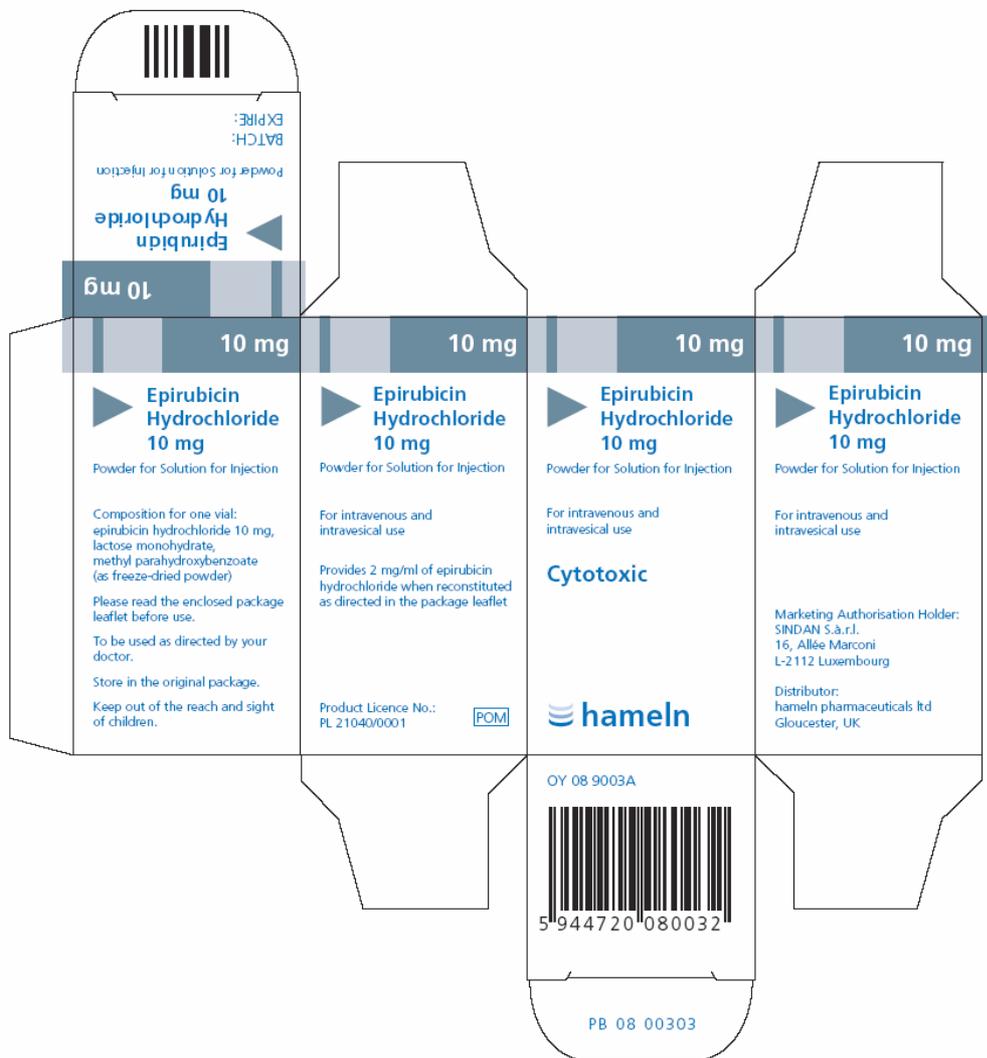
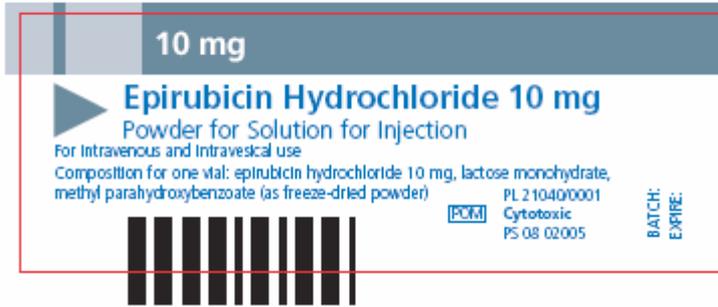
**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

18/01/2006

10 DATE OF REVISION OF THE TEXT

18/01/2006

Labels and Leaflet Epirubicin 10mg/vial for injection



Epirubicin Hydrochloride 10 mg Powder for Solution for Injection

epirubicin hydrochloride

A GUIDE FOR PATIENTS

Read all this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Epirubicin Hydrochloride 10 mg Powder for Solution for Injection is and what it is used for
2. Before you use Epirubicin Hydrochloride 10 mg Powder for Solution for Injection
3. How to use Epirubicin Hydrochloride 10 mg Powder for Solution for Injection
4. Possible side effects
5. Storing Epirubicin Hydrochloride 10 mg Powder for Solution for Injection
6. Further information

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection

The active substance is epirubicin hydrochloride 10 mg. The other ingredients are: lactose (monohydrate), methyl parahydroxybenzoate.

Marketing Authorisation Holder:

SINDANS .à.r.l.,
16, Allée Marconi, L-2112 Luxembourg.

Distributor:

hameln pharmaceuticals ltd
Gloucester
United Kingdom

Manufacturer(s):

Thymoorgan GmbH Pharmazie & Co. KG,
Schiffgraben 23, D-38690, Vienenburg, Germany.

S.C. SINDAN - PHARMA S.R.L.
11th, Ion Mihalache Blvd., 011171 Bucharest, Romania.

Product licence number: 21040/0001

1. WHAT EPIRUBICIN HYDROCHLORIDE 10 MG POWDER FOR SOLUTION FOR INJECTION IS AND WHAT IT IS USED FOR

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection is part of a group of medicines (anthracyclines) known as antineoplastic agents.

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection is a red-orange powder delivered in a colourless vial.

Each pack contains a single vial.

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection is used to treat a variety of cancers, either alone or in combination with other drugs. The way in which it is used depends upon the type of cancer that is being treated.

When injected into the bloodstream, Epirubicin Hydrochloride 10 mg Powder for Solution for Injection

has been found to be useful in the treatment of cancers of the breast, ovaries, stomach, bowel and lung. In addition, Epirubicin Hydrochloride 10 mg Powder for Solution for Injection can be given the same way to treat cancers of the blood forming tissues such as malignant lymphomas, leukaemias and multiple myeloma.

In addition, Epirubicin Hydrochloride 10 mg Powder for Solution for Injection can be injected into the bladder through a tube. This is sometimes used to treat abnormal cells or cancers of the bladder wall. It can also be used after other treatments to try and prevent such cells from growing again.

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection contains a medicine that acts upon cells that are actively growing, in such a way as to slow or stop their growth, and increasing the likelihood that the cells die. Cells that actively grow, such as those in cancer, are affected most by Epirubicin Hydrochloride 10 mg Powder for Solution for Injection treatment. This helps to selectively kill the cancer tissue rather than normal, healthy tissue.

2. BEFORE YOU USE EPIRUBICIN HYDROCHLORIDE 10 MG POWDER FOR SOLUTION FOR INJECTION

Do not use Epirubicin Hydrochloride 10 mg Powder for Solution for Injection

- if you are hypersensitive (allergic) to epirubicin hydrochloride or any of the other ingredients of Epirubicin Hydrochloride 10 mg Powder for Solution for Injection.
- if you are aware that your blood counts are too low, as Epirubicin Hydrochloride 10 mg Powder for Solution for Injection can lower them further.
- if you have been treated with certain kinds of chemotherapy - anthracycline drugs such as Epirubicin Hydrochloride 10 mg Powder for Solution for Injection come in different types, and previous treatment with others like doxorubicin or daunorubicin can increase the risk of side effects.
- if you have suffered from heart trouble in the past, or are presently receiving treatment for this.
- if you are sexually active, you are advised to use effective birth control to prevent pregnancy during treatment, whether you are male or female.
- if you are breast-feeding.

Take special care with Epirubicin Hydrochloride 10 mg Powder for Solution for Injection:

- if you are given medicines containing cimetidine.
- if your liver or kidneys are not working properly.
- if you are prescribed Epirubicin Hydrochloride 10 mg Powder for Solution for Injection it should only be given to you by doctors or nurses experienced in giving chemotherapy.

Pregnancy

Epirubicin hydrochloride - the active ingredient in Epirubicin Hydrochloride 10 mg Powder for Solution for Injection - may cause birth defects, it is important to tell your doctor if you think you are pregnant. Avoid becoming pregnant while you or your partner is being treated with Epirubicin Hydrochloride 10 mg Powder for Solution for Injection.

Breast-feeding

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

Because epirubicin hydrochloride may be harmful to nursing infants, women must discontinue breast-feeding before starting treatment with Epirubicin Hydrochloride 10 mg Powder for Solution for Injection.

Taking other medicines

Please inform your doctor or pharmacist

- If you are taking or have recently taken any other medicines, even those not prescribed.
- If you are given medicines containing cimetidine.

3. HOW TO USE EPIRUBICIN HYDROCHLORIDE 10 MG POWDER FOR SOLUTION FOR INJECTION

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection will be given to you by a doctor either in a drip (infusion) into a vein or directly into your bladder. Your doctor will decide what is the right amount to use (the dose) and the number of days treatment you should receive.

The dose is decided by taking into account the condition you have, your height and weight. From your height and weight the doctor will work out your body surface area; and it is this that your dose is calculated from.

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection made into a solution can also be put directly into the bladder to treat bladder cancer, or to help prevent it returning. The dose depends on the type of bladder cancer you have.

Your doctor will decide on the dose and number of day's treatment you receive depending on your condition and any other treatment you may receive.

While one course of treatment may sometimes be enough, more often your doctor will advise further courses in three or four weeks time. It may take several courses before your illness is under control and you feel better.

If you receive more Epirubicin Hydrochloride 10 mg Powder for Solution for Injection than you should:

You may notice sores in your mouth or the number of white blood cells and platelets (these help the blood to clot) in your blood may decrease. Should this happen, you may need antibiotics or blood transfusions. Mouth ulcers can be treated to make them less uncomfortable as they heal.

Heart damage can occur when high doses of Epirubicin Hydrochloride 10 mg Powder for Solution for Injection are given. This may not be detected for several weeks; so regular heart monitoring may be required for several weeks after your treatment has stopped.

4. POSSIBLE SIDE EFFECTS

All medicines have side effects, and Epirubicin Hydrochloride 10 mg Powder for Solution for Injection is no exception.

When you are being given Epirubicin Hydrochloride 10 mg Powder for Solution for Injection, if you feel pain, or a burning or stinging sensation at the place where the medicine goes into your vein you must tell your doctor immediately.

Allergic reactions can occur as the medicine is given - you may feel feverish, short of breath with a tight chest or throat, or dizzy should this occur. If this happens, tell your doctor or nurse immediately.

Between courses of treatment you may notice the following:

- Reddening of your urine, which is a normal occurrence related to the colour of the medicine, and should stop after a few days.
- Hair loss is common and may be quite severe. Beard growth may stop in men. Hair normally re-grows when the treatment course ends.
- Mouth ulcers can occur, and there may be a feeling of sickness (nausea), vomiting or diarrhoea.
- If you feel feverish, suffer chills or rashes it is important you tell your doctor, as you may be allergic to Epirubicin Hydrochloride 10 mg Powder for Solution for Injection.
- Your doctor should test your blood count during treatment to detect anaemia (a low red blood cell count) that can leave you feeling tired and lethargic.
- White blood cell counts can also drop, increasing the chance of infections and a raised temperature or fever.
- Different blood components called platelets can be affected making you bruise more easily, or bleed more than usual if you hurt yourself. It is important to seek medical advice if this happens.

When given in combination with other anti-cancer drugs, some patients have developed a secondary leukaemia after completing treatment. This is rare.

Epirubicin Hydrochloride 10 mg Powder for Solution for Injection used in the urinary bladder may be irritant to the bladder lining. This has been known to cause painful inflammation and sometimes bleeding into the urine. For the same reason a burning sensation may be felt when you pass urine. Let your doctor know if this occurs.

Your doctor will be making regular checks of:

- Your blood, to check for low blood cell counts that may need treatment.
- Your heart function, as Epirubicin Hydrochloride 10 mg Powder for Solution for Injection can have effects upon this.
- Your liver - again using blood tests - to check that Epirubicin Hydrochloride 10 mg Powder for Solution for Injection is not affecting the way it functions in a harmful way.

5. STORING EPIRUBICIN HYDROCHLORIDE 10 MG POWDER FOR SOLUTION FOR INJECTION

Store in the original package and protected from light.

Keep out of the reach and sight of children.

Your doctor must use the Epirubicin Hydrochloride 10 mg Powder for Solution for Injection solution as soon as it has been made. Vials, which have already been used, should be disposed of by your health professional. If Epirubicin Hydrochloride 10 mg Powder for Solution for Injection goes cloudy after preparation, then your health professional will dispose of it safely.

6. FURTHER INFORMATION

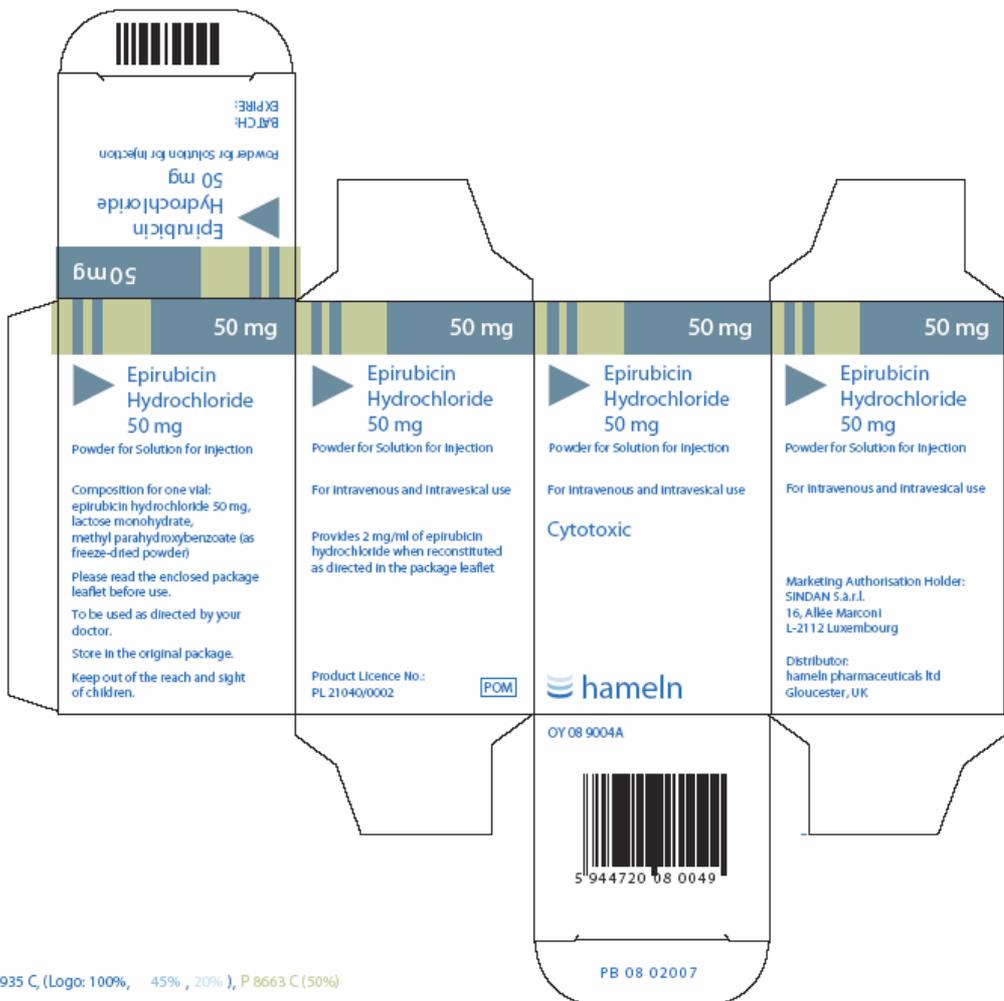
For any further information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

SINDAN S.à.r.l
16, Allée Marconi L-2112 Luxembourg.

This leaflet was prepared in **October 2005**.

PL 08 02006

Labels and Leaflet Epirubicin 50mg/vial



2935 C, (Logo: 100%, 45%, 20%), P 8663 C (50%)

Epirubicin Hydrochloride 50 mg Powder for Solution for Injection

epirubicin hydrochloride

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The active substance is epirubicin hydrochloride 50 mg. The other ingredients are: lactose (monohydrate), methyl parahydroxybenzoate.

Marketing Authorisation Holder:

SINDAN S.à.r.l.,
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Distributor:

hameln pharmaceuticals ltd
Gloucester
United Kingdom

Manufacturer(s):

Thymoorgan GmbH Pharmazie & Co. KG,
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S.C. SINDAN - PHARMA S.R.L.
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PL 08 02009