

Public Assessment Report
Mutual Recognition Procedure

**Epirubicin Hydrochloride 2mg/ml Solution for
Injection/Intravesical Use**

MRP no: UK/H/868/01
UK licence no: PL 04515/0160

Applicant: Mayne Pharma Plc

Epirubicin Hydrochloride 2mg/ml Solution for Injection/Intravesical Use

LAY SUMMARY

Estonia, the Netherlands, Norway and Sweden today granted Mayne Pharma Plc Marketing Authorisations (licences) for the medicinal products Epirubicin Hydrochloride 2mg/ml Solution for Injection/Intravesical Use (PL 04515/0160). These are prescription-only medicines (POM) used in the treatment of cancer of the breast, cancer of the stomach and to help prevent recurrence of bladder cancer after surgery.

Epirubicin Hydrochloride 2mg/ml Solution for Injection/Intravesical Use contains the active ingredient epirubicin hydrochloride, which is an anti-cancer medicine, sometimes called chemotherapy.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Epirubicin Hydrochloride 2mg/ml Solution for Injection/Intravesical Use outweigh the risks, hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 4
Module 2: Summary of Product Characteristics	Page 5
Module 3: Product Information Leaflet	Page 12
Module 4: Labelling	Page 17
Module 5: Scientific Discussion	Page 21
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6 Steps take after initial procedure	Not applicable

Module 1

Product Name	Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use
Type of Application	Abridged Initial application Generic, Article 10.1 [formerly 10.1(a)(iii)] Chemical substance Prescription only
Active Substance	Epirubicin Hydrochloride
Form	Solution for Injection/Intravesical Use
Strength	2mg/ml
MA Holder	Mayne Pharma Plc
RMS	United Kingdom
CMS	Estonia, the Netherlands, Norway, Sweden
Procedure Number	UK/H/868/01
Timetable	Day 90 14/06/2006

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre contains 2 mg epirubicin hydrochloride. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection (Injection)/Intravesical Use.

A clear red solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous use:

- Breast carcinoma
- Gastric carcinoma

Intravesical use:

- Prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

Epirubicin is for intravenous or intravesical use only.

Intravenous administration

It is advisable to administer epirubicin via the tubing of a free-running intravenous saline infusion after checking that the needle is properly placed in the vein. Care should be taken to avoid extravasation (see Section 4.4).

Conventional dose

When epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body area. Epirubicin should be injected intravenously over 3-5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematomedullary status.

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 dose

Epirubicin as a single agent for the high dose treatment of breast cancer should be administered according to the following regimens:

- 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 5fluorouracil and oral tamoxifen, are recommended.

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

Lower doses (60-75 mg/m² for conventional treatment and 105-120 mg/m² for high dose treatment) are recommended for patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

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

Cancer Indication	Epirubicin Dose (mg/m ²) ^a	
	Monotherapy	Combination Therapy
Gastric cancer	60–90	50

^aDoses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals

Combination therapy

If epirubicin is used in combination with other cytotoxic products, the dose should be reduced accordingly. Commonly used doses are shown in the table above.

Impaired liver function

The major route of elimination of epirubicin is the hepatobiliary system. In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:

Serum Bilirubin	AST*	Dose Reduction
1.4 – 3 mg/100 ml		50%
> 3 mg/100 ml	> 4 times upper normal limit	75%

*AST – aspartate aminotransferase

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. Lower starting doses should be considered in patients with severe renal impairment (serum creatinine >450µmol/l).

Intravesical administration

Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations.

For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at the same dose.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

Dose Epirubicin required	Volume of 2 mg/ml epirubicin injection	Volume of diluent sterile water for injection or 0.9% sterile saline	Total volume for bladder installation
50 mg	25 ml	25 ml	50 ml

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 urine at the end of the instillation time.

4.3 Contraindications

Epirubicin is contraindicated in:

- Patients who have demonstrated hypersensitivity to epirubicin, other anthracyclines or to 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.
- Lactation

When administered intravesically:

- Invasive tumours that have penetrated the bladder wall
- Urinary tract infection
- Inflammation in the urinary tract/bladder
- Catheterisation problems.

4.4 Special warnings and special 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 management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

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

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

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

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

Cardiomyopathy induced by anthracyclines is associated with 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 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.

Heart failure may appear several weeks after discontinuing therapy with epirubicin and may be unresponsive to specific medical treatment. The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area.

Epirubicin is mainly eliminated via the liver. Therefore it is necessary to evaluate liver function (AST, ALT, alkaline phosphatase, bilirubin) prior to initiating treatment and during treatment. In patients with increased bilirubin levels or AST epirubicin clearance can be reduced, which may lead to increased toxicity. For these patients a dose reduction is recommended (see section 4.2). For patients with reduced renal function serum creatinine levels should be checked regularly prior to and during treatment. For patients with increased serum creatinine (>450µmol/l) a dose reduction is proposed (see section 4.2).

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 checked so that this phenomenon may be recognised and properly managed.

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

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin can be used in combination with other anti-cancer agents but patients should be monitored for additive toxicity. Concomitant use of other medicinal products that may be cardiotoxic or affect cardiac function should be monitored throughout treatment. 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.

Cardiotoxicity of epirubicin is enhanced by certain radiotherapeutic treatments and by previous or concomitant use of other anthracycline derivatives like mitomycin-C, dacarbazine, dactinomycin and possibly cyclophosphamide. Epirubicin can potentiate the effect of radiation. Medicinal products that induce the cytochrome P450 system (e.g., rifampicin and barbiturates) can enhance epirubicin metabolism, with consequently reduced efficacy. Conversely, certain medicinal products (e.g. cimetidine) can potentiate the clinical effect of epirubicin by inhibiting its metabolism.

Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon α 2b, 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-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity.

4.6 Pregnancy and lactation

Epirubicin is a potential teratogen and if administered to pregnant women may cause miscarriage, embryotoxicity and foetal death. During pregnancy, particularly the first trimester, cytostatic drugs should only be used on strict indication and when the potential benefits to the mother have been weighed against possible risks to the foetus. Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during epirubicin therapy, and use effective contraception during treatment with epirubicin.

It is unknown whether epirubicin is excreted in human breast milk. A risk to the breast-feeding infant cannot be excluded. Breast-feeding should be discontinued during treatment with epirubicin.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse event frequencies have been categorised as follows: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000 including isolated reports).

Neoplasms benign, malignant and unspecified (including cysts and polyps): Rare: The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemias have a short (1-3 year) latency.

Blood and the lymphatic system disorders:

Common: Myelosuppression.

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 no different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm³ for < 7 days) which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

Immune system disorders:

Rare: Anaphylaxis

Cardiac disorders:

Rare: Cardiotoxicity (see Section 4.4).

Gastrointestinal disorders:

Common: Nausea, vomiting and diarrhoea have also been reported.

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.

Rare: Urticaria

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, mainly along the side of the tongue and the sublingual mucosa.

Rare: Fever and chills have been reported rarely.

Injury, poisoning and procedural complications:

Common: Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration.

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: 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).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after intravenous 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 consistently lower and virtually parallel those of the unchanged drug.

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. The drug does not cross the blood brain barrier.

5.3 Preclinical safety data

Epirubicin, as other anthracyclines and cytotoxic drugs, has been shown to be genotoxic in in vitro and in in vivo studies as well as carcinogenic in rat. Epirubicin is toxic to reproductive organs and embryotoxic in rat. No malformations were evident in rat or rabbit. Epirubicin, as other anthracyclines and cytotoxic drugs, should be considered a potential teratogen. Peri/postnatal studies in rat indicate adverse effects on the offspring at clinical doses. It is not known whether epirubicin is excreted in breast milk. Animal studies indicate that epirubicin has a more favourable therapeutic index and a lower systemic and cardiac toxicity than doxorubicin.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Water for Injections

Hydrochloric acid for pH adjustment

MHRA; Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use MRPAR

6.2 Incompatibilities

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug, which includes sodium bicarbonate containing solutions. Only the diluents detailed in section 6.3 should be used.

Neither the injection nor any diluted solution should be mixed with any other drugs. (A physical incompatibility with heparin has been reported).

Epirubicin should not be mixed with other drugs.

6.3 Shelf life

Clear glass and ONCO-TAIN® vials: 2 years

In use: Epirubicin Hydrochloride 2 mg/ml Injection may be further diluted, under aseptic conditions, in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. The infusion solution is chemically stable when stored in PVC infusion bags, prepared under full aseptically controlled conditions, for 14 days at 25°C ± 2°C or for 28 days at 2-8°C in the absence of light. From a microbiological point of view however, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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

For 'in use' storage conditions, see section 6.3.

6.5 Nature and contents of container

Epirubicin Hydrochloride 2 mg/ml Injection is supplied in clear Type I glass vials with a rubber (chlorobutyl) stopper. Vials may be wrapped in a protective plastic (ONCO-TAINED®). The vials contain 5ml, 25ml, 50ml or 100ml of sterile solution of epirubicin hydrochloride 2 mg/ml. These are supplied in both individually packed single vials and packs of 5 vials.

Not all packs may be marketed.

6.6 Special precautions for disposal

Epirubicin Hydrochloride 2 mg/ml 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 portion of the vial should be discarded immediately.

Guidelines for the safe handling and disposal of antineoplastic agents:

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

7. MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW

8. MARKETING AUTHORISATION NUMBER

PL 04515/0160

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Module 3

Product Information Leaflet & Technical Leaflet

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you are given this medicine.
 Keep this leaflet. You may want to read it again.
 If you have any questions, ask your doctor or pharmacist.
 If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use (Epirubicin Hydrochloride)

In this leaflet:

1. What Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use is and what it is used for
2. Before you use Epirubicin Hydrochloride Solution for Injection/Intravesical Use
3. How to use Epirubicin Hydrochloride Solution for Injection/Intravesical Use
4. Possible side effects
5. How to store Epirubicin Hydrochloride Solution for Injection/Intravesical Use
6. Further information

1. What Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use is and what it is used for?

Epirubicin Hydrochloride Solution for Injection/Intravesical Use is an anti-cancer medicine. Treatment with an anti-cancer medicine is sometimes called cancer chemotherapy.

Epirubicin hydrochloride is used in the treatment of:

- Cancer of the breast
- Cancer of the stomach

Epirubicin hydrochloride Solution for injection/intravesical use is also used to help prevent recurrence of bladder cancer after surgery.

2. Before you use Epirubicin Hydrochloride Solution for Injection/Intravesical Use

Do not use this medicine:

- if you are allergic (hypersensitive) to epirubicin, similar medicines (called anthracyclines – see below) or any of the other ingredients of epirubicin hydrochloride solution for injection/intravesical use
- if you have fewer blood cells than normal. Your doctor will check this
- 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 drugs as epirubicin hydrochloride solution for injection/intravesical use (called anthracyclines). They have similar side effects (including those effects on the heart).
- if you have suffered or currently have problems with your heart
- if you are breast-feeding

When administered intravesically (directly into the bladder), epirubicin hydrochloride solution for injection/intravesical use should not be used if:

- the cancer has penetrated the bladder wall
- you have an infection in your urine tract
- you have pain or inflammation in your bladder

- your doctor has problems inserting a catheter (tube) into your bladder

Special care will be taken:

- to make sure the number of cells in your blood does not drop too low. Your doctor will check this regularly.
- to check the level of uric acid in your blood. Your doctor will check this.
- if you have liver disease
- if you have kidney disease
- to make sure your heart is working properly. Your doctor will check this regularly.
- if you have received or are receiving radiotherapy to the chest area.

Using other medicine:

Special care will also be taken if you are taking any of the following medicines:

- other medicines that may affect your heart for example, other cancer treatments such as mitomycin-C, dacarbazine, dactinomycin and possibly cyclophosphamide and radiotherapy.
- Other medicines that may affect your liver e.g. barbiturates (drugs used in epilepsy or sleep disorders) and rifampicin (a drug used to treat TB)
- cimetidine (a drug used to reduce the acid in your stomach)
- paclitaxel and docetaxel (drugs used in some cancers)
- interferon alpha-2b (a drug used in some cancers and lymphomas and for some forms of hepatitis)
- quinine (drug used for treatment of malaria and for leg cramps)
- dexrazoxane (a drug sometimes used with doxorubicin to reduce the risk of heart problems)
- dexverapamil (a drug used to treat some heart conditions).

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

Pregnancy and breast-feeding

Epirubicin hydrochloride solution for injection/intravesical use can cause severe harm to the unborn baby and effective contraception should be used during treatment. If you are pregnant or become pregnant whilst receiving epirubicin you should inform your doctor immediately.

You must not use epirubicin hydrochloride solution for injection/intravesical use if you are breast-feeding.

Driving and using machines

You may feel and/or be sick after being given this medicine, therefore special care should be taken when driving or using machines.

3. How to use Epirubicin Hydrochloride Solution for Injection/Intravesical Use

The dose of medicine given to you will depend on the type of cancer you have, your health, how well your liver is working and any other medicines you may be taking.

By injection or infusion into a vein

The medicine will be given to you as an injection into a vein over 3-5 minutes. Or it may be diluted with glucose (sugar solution) or sodium chloride (salt water) before it is given slowly, usually via a drip into a vein over 30 minutes. If the drip comes loose or the solution is leaking from the vein, you must tell the nurse or doctor immediately. You may be given another dose of this medicine in 3 weeks.

By being put into the bladder (intravesical administration)

The medicine may be given directly into the bladder using a catheter. If this method 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 medicine solution should be kept in your bladder for 1 hour after being given. You will need to alter your position occasionally to ensure that the medicine reaches all parts of your bladder.

When emptying your bladder after the medicine has been given, take care that your urine does not come into contact with your skin. In case contact does happen, thoroughly wash the affected area with soap and water but do not scrub.

While you are receiving epirubicin hydrochloride solution for injection/intravesical use your doctor will take regular blood tests. This is to measure the effect the drug is having. Your doctor will also do regular tests on how your heart is working.

If the medicine has been added to a bag of fluid for injection, or to be given into the bladder, it should be labelled with the strength of the drug, volume and the time after which it should not be used.

If you use more Epirubicin Hydrochloride Solution for Injection/Intravesical Use than you should: As this medicine will be given to you while you are in hospital it is unlikely that you will be given too little or too much. However, tell your doctor or pharmacist if you have any concerns.

4. Possible Side Effects

Like all medicines, epirubicin hydrochloride solution for injection/intravesical use can cause side effects, although not everybody gets them.

If any of the following rare side effects occur when epirubicin hydrochloride solution for injection/intravesical use is given by infusion into a vein, tell your doctor immediately:

- if there is any redness, pain or swelling where the injection has been given
- you have chest pains, shortness of breath or swelling of your ankles (these effects may occur up to several weeks after finishing treatment with epirubicin)
- if you have a severe allergic reaction, noticed by feeling faint, skin rash, swelling of the face and difficulty in breathing or wheeze. In some cases collapse may occur.

These are very serious side effects. You may need urgent medical attention.

You may notice other side effects after the medicine has been given into a vein.

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

Very common (occurs in more than 1 of 10 users)

- loss of hair
- reduced growth of facial hair

Common (occurs in more than 1 of 100 but less than 1 of 10 users)

- feeling or being sick
- swelling or pain in your mouth
- ulcers on the lips or tongue or under the tongue
- diarrhoea

Rare (occurs in more than 1 of 10,000 but less than 1 of 1,000 users)

- fever or chills
- hives (urticaria).

Your urine may be red in colour for a couple of days after being given epirubicin.

This medicine may also affect your heart function (this occurs rarely)-and commonly the number of blood cells (for example red cells, white cells and platelets). Liver function may also be affected. As a long term consequence, a type of leukaemia (acute myeloid leukaemia) has been reported rarely. Your doctor will give you regular heart and blood tests to check for these effects.

If this medicine is injected directly into the bladder, a common side effect is difficulty or pain when passing urine. You may also see blood in your urine. If you notice any of these side effects, tell 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 or pharmacist.

5. How to store Epirubicin Hydrochloride Solution for Injection/Intravesical Use

Keep out of the reach and sight of children.

Store in a refrigerator (2°C – 8°C).

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

Epirubicin hydrochloride, when diluted in either glucose 5% or sodium chloride 0.9%, should not normally be stored for longer than 24 hours in a fridge.

Do not use after the expiry date printed on the vial label and carton.

6. Further Information

What epirubicin hydrochloride solution for injection/intravesical use contains

The active substance is epirubicin hydrochloride. Each millilitre contains 2 milligrams of epirubicin hydrochloride.

The other ingredients are sodium chloride, water for injections and hydrochloric acid used as a pH adjuster.

What epirubicin hydrochloride solution for injection/intravesical use looks like and contents of the pack

Epirubicin Hydrochloride 2 mg/ml injection is a clear red solution for injection or intravesical use.

Each millilitre (ml) of solution contains 2 milligrams (mg) of epirubicin hydrochloride. The medicine comes in glass containers called vials with rubber closures, containing 10 mg (5 ml), 50 mg (25 ml), 100 mg (50 ml) and 200 mg (100 ml) of epirubicin hydrochloride.

The vials may be wrapped in a protective plastic to reduce the risk of spillage if the vials break; these are referred to as ONCO-TAIN®.

The vials are available in single or 5 vial packs of 5 ml, 25 ml, 50 ml or 100 ml. Not all pack sizes may be marketed.

Marketing authorisation holder and manufacturer: Mayne Pharma Plc, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, United Kingdom.

This leaflet was last approved in

The following information is intended for medical or healthcare professionals only:

For Intravenous Injection and Intravesical Administration

Incompatibilities

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug, which includes sodium bicarbonate containing solutions. Only the diluents detailed in 'Dilution Instructions' should be used.

Neither the injection nor any diluted solution should be mixed with any other drugs. (A physical incompatibility with heparin has been reported).

Dilution Instructions

The injection may be given via the tubing of a free-running intravenous saline infusion. Where the injection is to be administered after dilution, the following instructions should be followed.

Epirubicin Hydrochloride solution for injection/intravesical use may be diluted under aseptic conditions 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 portion of the vial should be discarded immediately.

Safe Handling

This is a cytotoxic product, please follow your local policy guidelines for instructions on the safe handling/disposal of cytotoxics.

Storage

Store at 2-8°C.
Keep container in the outer carton.

In use: Epirubicin Hydrochloride 2 mg/ml solution for injection/intravesical use may be further diluted as detailed above. The infusion solution is chemically stable when stored in PVC infusion bags prepared under full aseptically controlled conditions for 14 days at 25°C ± 2°C or for 28 days at 2-8°C in the absence of light. From a microbiological point of view however, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

Marketing Authorisation Holder

Mayne Pharma Plc
Warwickshire, CV31 3RW
UK

This leaflet was last approved in mm/yyyy

Module 4

Labelling

TEXT FOR OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 50 ml contains epirubicin hydrochloride 100 mg

3. LIST OF EXCIPIENTS

Sodium chloride, hydrochloric acid and Water for Injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for Injection/Intravesical Use
100 mg in 50 ml
1 x 50 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For Intravenous or Intravesical Use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

N/A

8. EXPIRY DATE

Expiry will be included at the time of packaging

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Keep container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not Applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc
Warwickshire, CV31 3RW
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 04515/0160

13. MANUFACTURER'S BATCH NUMBER

Batch number will be included on the labels at the time of packaging

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

To be used as directed by a medical practitioner.
For single use. Discard any unused contents.

TEXT FOR VIAL LABEL**1. NAME OF THE MEDICINAL PRODUCT**

Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use

4. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 50 ml contains epirubicin hydrochloride 100 mg

5. LIST OF EXCIPIENTS

Sodium chloride, hydrochloric acid and Water for Injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for Injection/Intravesical Use
100 mg in 50 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For Intravenous or Intravesical Use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

N/A

8. EXPIRY DATE

Expiry will be included at the time of packaging

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not Applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc
CV31 3RW
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 04515/0160

13. MANUFACTURER'S BATCH NUMBER

Batch number will be included on the labels at the time of packaging

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally

15. INSTRUCTIONS ON USE

To be used as directed by a medical practitioner.
For single use. Discard any unused contents.

Module 5

Scientific discussion during initial procedure

1. INTRODUCTION

Background

This application was submitted by Mayne Pharma Plc for a generic version of Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use, via the Decentralised (Mutual Recognition) Procedure. The originator product is Farmorubicin Solution for Injection 10mg licensed to Pharmacia (Denmark) on 25/06/85.

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use could be approved in the treatment of the following indications:

Intravenous use:

- Breast carcinoma
- Gastric carcinoma

Intravesical use:

- Prophylaxis of recurrences after transurethral resection.

Marketing Authorisations were granted in Estonia, The Netherlands, Norway and Sweden. The product names in these CMS's are:

Estonia:	Epirubicin Mayne 2mg/ml
Norway:	Epirubicin Mayne 2mg/ml Injksjonvæske, oppløsning
Netherlands:	Epirubicine 2mg/ml Mayne, oplossing voor injectie
Sweden:	Epirubicin Mayne 2mg/ml, Injektionsvätska, lösning

Overall Benefit/Risk Assessment

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. No bioequivalence study was carried out as the products are for intravenous use.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

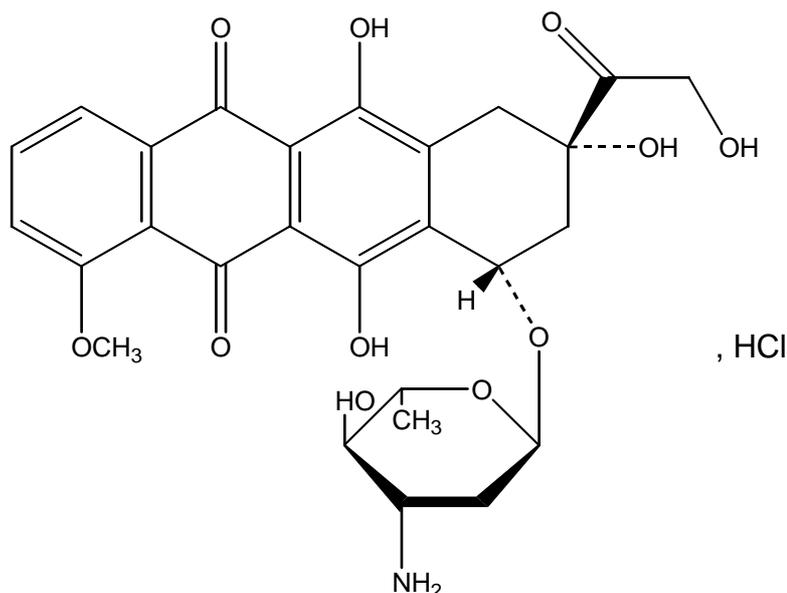
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has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

2. QUALITY ASPECTS

3.2.S DRUG SUBSTANCE

A PhEur Certificate of Suitability has been supplied for this source of active substance.

The structure is given below



3.2.S.4 Control of Drug Substance

The drug substance will be tested according to the PhEur monograph for epirubicin hydrochloride. The certificate of suitability also includes a test for residual solvents and an additional potential impurity.

3.2.S.4.4.2 Batch Analyses – Drug Product Manufacturer

The drug product manufacturer tests to *Ph Eur* standards.

3.2.S.5 Reference Standards or Materials

The active substance manufacturer's standards are covered by the Certificate of Suitability and where the finished product manufacturer uses secondary standards, these are calibrated against a *Ph Eur* primary reference standard.

3.2.S.7 Stability

The active substance manufacturer has tested batches made over a period of April, July and December 2001.

Stability testing is carried out at $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $15^{\circ}\text{C} \pm 2^{\circ}\text{C}$.

The active substance manufacturer has given the bulk drug a re-test period of 2 years. There is no evidence of any change in the stability data for 4°C , provided to date.

The water limit in the specification is that of the Ph.Eur.

There is no issue re stability.

The active substance manufacturer has committed to perform bioburden testing at the final timepoint in the stability calendar.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The product is presented in one strength, 2mg/ml, in 10, 50, 100 and 200mg sizes i.e. from 5ml to 100ml.

Component	Reference
Active ingredient	
Epirubicin hydrochloride	Ph. Eur.
Excipients	
Sodium Chloride	Ph. Eur./ BP/USP
Water for Injection	Ph. Eur./ BP/USP
Hydrochloric acid (1N)	Ph. Eur./ BP/NF
Nitrogen	Ph. Eur./ BP/NF

3.2.P.2 Pharmaceutical Development

Epirubicin is unique among the anthracycline cytotoxic antibiotics in being a glucuronide. The active ingredient complies with the monograph in the European Pharmacopoeia and is present in the same concentration as the European innovator product.

This formulation contains the same excipients as the innovator. Given that the innovator has marketed Pharmorubicin[®] for many years it is considered that the compatibility between the active substance and the excipients is well established. This has also been confirmed through the stability testing of the finished product.

All the excipients are commonly used and well characterised, they all conform to their monographs in the European Pharmacopoeia.

Formulation development

The Company state the formulation is the same as the innovator's, and hence is acceptable. Given the nature of the product and its formulation, that is a reasonable

conclusion. Comparison between the innovator's product Pharmorubicin and this one was carried out.

Mayne Pharma's Epirubicin hydrochloride Injection and Pharmacia's Pharmorubicin[®] demonstrated practically identical results for appearance and pH. All results are within the proposed specifications. The impurity profiles of Epirubicin hydrochloride Injection and Pharmorubicin[®] are similar when the age of the Pharmacia samples are taken into consideration. The Pharmacia samples are approximately 18 months older than the Epirubicin hydrochloride Injection samples, hence higher impurity levels are expected in the Pharmacia samples.

Consequently, the two products, Mayne Pharma's Epirubicin hydrochloride Injection and Pharmacia's Pharmorubicin[®] are considered to be essentially equivalent.

No bioequivalence studies were carried out. That is acceptable, given the fact that it is a solution given by injection, and the formulations are the same.

The finished product is a sterile solution.

Choice of container: all containers are of Type 1 glass as defined by the USP/Ph.Eur.

Choice of closure: for all presentations a rubber (chlorobutyl) closure is used (as defined by the Ph.Eur).

It is proposed, as an option, to shrink wrap a protective PET sleeve over the final sealed and labelled container. The shrink wrapped vials (or ONCO-TAIN[®] vials) are preferred to ampoules for the following reasons:

- There is a reduced risk of operator contamination compared to glass ampoules.
- Vials are invariably stronger containers than glass ampoules.
- The shrink-wrapping provides added resistance to breakage; and
- Product containment upon breakage.

The quality summary contains the following information:

"The product is manufactured and filled into the glass vial, after labelling and before packing into the carton, the vial is conveyed through the Sleeve Shrinking Equipment (SSE), this heat shrink-wraps the additional plastic sleeve onto the container.

Temperature rise studies have been performed in order to determine the temperature that a finished product would typically experience during the sheathing process. The results indicated that the sheathing process is not expected to compromise the integrity of the product.

In a further study, non-ONCO-TAINED[®] samples were compared against ONCO-TAINED[®] samples. No significant difference in the results for potency or impurity profile was observed, indicating that the ONCO-TAINING process does not affect the product. This is also confirmed through stability testing of the Epirubicin hydrochloride Injection batches (ONCO-TAINED[®]).

Test data on a 100ml presentation pre- and post- sheathing is provided and is satisfactory.

Mayne has conducted studies to show compatibility with glucose 5% & 0.9% NaCl at 2-8°C at room temperature. The brand leader Pharmorubicin SPC states that the product should be injected via a flowing infusion, which is what is recommended here.

3.2.P.3 Manufacture

The batch formulae for the various vial sizes have been provided and are satisfactory.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

In-Process Specifications have been provided and are acceptable.

The method for assaying the drug as an in process control is given. Suitable experimental details are provided.

In-process batch data for all 3 vial sizes are provided. All bioburden values were satisfactory.

3.2.P.3.5 Process Validation

It is stated the validation of the manufacturing process is an on-going process, which continues to commercialisation.

3.2.P.4 Control of Excipients

The applicant has stated that the nitrogen used is in compliance with the Ph Eur monograph for nitrogen (medicinal use). This is considered acceptable as Epirubicin Hydrochloride Injection is not considered to be an oxygen sensitive product.

A general statement is made that the NaCl, HCl, WFI and nitrogen meet *Ph Eur* requirements as up dated. The applicant confirms that the water for injections complies with the Ph. Eur. requirements, including the limits for bacterial endotoxins and that the water for injections is made by distillation in accordance with the Ph. Eur. requirements.

No excipients of human or animal origin are used in this product.

3.2.P.5 Control of Drug Product

The Applicant has compared the related substances they have chosen to control, as they are present and increase on storage, in the drug substance, and the product at release and end of shelf life. The proposed limits for release in the light of batch data have been discussed, in respect of the supporting batch data.

The limit for individual unknowns meets ICH guidelines.

3.2.P.5.1 Specification

The specification has been provided. The comparative product data does not indicate that the impurity profiles are different for the 2 sets of products.

The Company indicate in the absence of a *BP* monograph for the injection, the general *Ph Eur/BP* injection monograph and Q6A – new drugs –chemicals guidance and stability data have been used to set specifications.

3.2.P.5.2 Analytical Procedures

An in-house HPLC method is to be used for potency, identification and related substances. All other procedures are *Ph Eur*. The sterility test uses a membrane method, and endotoxins are determined using the gel clot method.

3.2.P.5.3 Validation of Analytical Procedures

Validation reports for in-house analytical methods for assay and related substances are provided. Also provided are the validation reports for the methods used for the determination of bacterial endotoxins (LAL) and sterility, which are performed in accordance with *Ph. Eur.* requirements.

A report is provided for the HPLC methods, and it is covered in the quality summary. Both the assay and related-substances methods were validated satisfactorily. Forced degradation studies were performed.

An assurance has been given that the *Ph Eur* sterility test validation will be re-validated using the organisms cited in the current *Ph Eur* 4th edition sterility test.

3.2.P.5.4 Batch Analyses.

Batches of the 10mg/5ml, 50mg/25ml and 200 mg/100 ml presentations have been manufactured by the finished product manufacturer. No batches of the proposed 100mg/50ml presentation have been manufactured for stability testing, as these are bracketed by the smallest and largest strength presentations

3.2.P.5.5 Characterisation of Impurities

Doxorubicinone and epirubicin dimer are listed in the Epirubicin Hydrochloride *Ph. Eur.* monograph. Doxorubicinone and epirubicin dimer have been identified in the drug product by chromatographic retention times. The impurities doxorubicin, daunorubicinone, epidaunorubicin and dihydrodaunorubicin which are also listed in the Epirubicin Hydrochloride *Ph. Eur.* monograph, have not been listed in the drug product specification as they are drug substance manufacturing impurities. Therefore, they will be controlled in the drug substance.

Satisfactory limits for impurities have been included in the specification.

3.2.P.5.6 Justification of Specifications

There is no USP/BP monograph for Epirubicin hydrochloride Injection. The proposed specifications are therefore based upon the USP requirements for Injections <1>, the

BP/Ph.Eur requirements for Parenteral Preparations and in accordance with the ICH guideline ICH 6A, *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*.

pH: The proposed specification is based on testing of the innovator's product, and on stability testing of the exhibit batches.

The assay specification is proposed based on stability testing of the exhibit batches, and testing of the innovator product.

Two identification tests have been proposed. These are acceptable.

3.2.P.6 Reference Standards or Materials

The Applicant has provided a table of the standards used. These include *Ph Eur* standards for epirubicin HCl, and related substances. In addition active substance manufacturer batches of epirubicin HCl and related substances are also used as standards.

3.2.P.7 Container Closure System

The product is packed in clear Type 1 Glass vials with a chlorobutyl closure. The vials are stated to comply with *Ph Eur/ BP/ USP* requirements. The closure meets the requirements of the *USP* for toxicity tests. They meet *Ph Eur* Type 1 closure requirements.

The presentations are 10mg/5ml; 50mg/25ml (packed in a 30ml vial); 100mg/50ml; 200mg/100ml.

Adequate testing has been performed on the container closure system.

3.2.P.8 Stability

Please note, only batches of the 10 mg/5 mL, 50 mg/25 mL and 200 mg/100 mL were placed on stability. No batches of the 100 mg/50 mL presentation have been manufactured, as this is bracketed by the smallest and largest strength presentations. A bracketing justification is provided and is acceptable.

The formulations used are the commercial ones.

The planned stability studies were carried out at 2-8°C. Depending upon the time point, either inverted or upright or both types of samples were tested. Assay, pH, related substances were tested for at all times. Sterility and endotoxins were also tested at appropriate intervals.

Accelerated testing conditions used were 25°C/60%RH. Assay, pH, related substances were tested for at all times. Testing at 15°C for 12 months was also used, as was freezer temperature.

The test procedures were those to be used for the commercial product.

Stability Test Results

The quality summary states that freezing did not produce a problem. Batches stored at 2-8°C met the specification. Storage at 15°C showed batches met specification, but impurities were increasing. Batches stored at 25°C showed degradation.

The quality summary report states that the data support a 24 month shelf-life at 2-8°C.

Over the 24 month period all assay results were within the specification limits.

All results for total related substances remained within the specification at both 2 – 8°C and 15°C. The limit for total impurities (including all process impurities) is based on the data observed during stability testing of the exhibit batches, and in consideration of the limit of total impurities in the drug substance. Some allowance has also been made for manufacturing variability. The limits are acceptable.

The finished product manufacturer has committed to performing stability studies on the first two commercial batches of Epirubicin Hydrochloride Injection. If stability problems occur, the authorities will be notified.

Stability Data on Diluted Product in Infusion or Injection Systems

Infusion study

Epirubicin hydrochloride Injection may be diluted further with either 0.9% Sodium Chloride (NaCl) or 5% Glucose Solution prior to administration by iv infusion. Epirubicin hydrochloride Injection may also be stored undiluted in polypropylene syringes at a concentration of 2 mg/ml. Therefore an infusion study was carried out.

Samples of solutions were analysed for appearance, pH, potency, related substances and particulate matter.

Based on the data provided the following in-use shelf lives are proposed:

1. A 14 day in use shelf life is proposed for Epirubicin hydrochloride Injection diluted to 0.2 mg/ml and 1.0 mg/ml in infusion bags when stored at 25±2°C in the presence of light.
2. A 28 day in use shelf life is proposed for Epirubicin hydrochloride Injection diluted to 0.2 mg/ml and 1.0 mg/ml in infusion bags when stored at 2 - 8°C in the absence of light.
3. A 28 day in use shelf life is proposed for Epirubicin hydrochloride Injection 2 mg/ml when stored in polypropylene syringes at 2 - 8°C in the absence of light and 25±2°C in the presence of light.

No data on the stability of the drug in infusion fluids or syringes is provided in the UK essentially similar product's SPC. The suppliers of the syringes and infusion bags have been provided. The syringes were CE marked and available in the UK.

Epirubicin is a tetracyclic compound which may act as an extractant. The finished product manufacturer acknowledges there is the potential for additives (particularly

diethyl hexyl phthalate) to leach from the PVC infusion bags. Hence, they commit to performing a leaching study prior to release of the first commercial batch and an acceptable DEHP protocol has been provided.

3.2.R Regional information

This issue is covered by the certificate of suitability.

SPC, LABELS AND PACKAGE LEAFLET

SPC, Labels and leaflet were supplied and are satisfactory.

PHARMACEUTICAL CONCLUSIONS

Product Licences for these preparations can be granted.

3. NON-CLINICAL ASPECTS

This application for a generic product claims essential similarity to Pharmorubicin 2mg/ml Injection licensed to Pharmacia, which has been licensed within the UK for over 10 years.

No new preclinical data has been supplied with these applications, however, a preclinical expert report summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

4. CLINICAL ASPECTS

1. INTRODUCTION AND BACKGROUND

This is an application for Epirubicin Hydrochloride 2mg/ml Solution for Injection/Intravesical Use for the treatment of a range of neoplastic conditions by the intravenous and intravesical routes.

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

The applicant has submitted the following:

Intravenous use:

- Breast carcinoma
- Gastric carcinoma

Intravesical use:

- Prophylaxis of recurrences after transurethral resection.

3. DOSE & DOSE SCHEDULE

The applicant has submitted the following:

Epirubicin is for intravenous or intravesical use only.

Intravenous administration

It is advisable to administer epirubicin via the tubing of a free-running intravenous saline infusion after checking that the needle is properly placed in the vein. Care should be taken to avoid extravasation (see Section 4.4).

Conventional dose

When epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body area. Epirubicin should be injected intravenously over 3-5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematomedullary status.

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 dose

Epirubicin as a single agent for the high dose treatment of breast cancer should be administered according to the following regimens:

- 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 5fluorouracil and oral tamoxifen, are recommended.

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

Lower doses (60-75 mg/m² for conventional treatment and 105-120 mg/m² for high dose treatment) are recommended for patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

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

Cancer Indication	Epirubicin Dose (mg/m ²) ^a	
	Monotherapy	Combination Therapy
Gastric cancer	60-90	50

^aDoses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals

Combination therapy

If epirubicin is used in combination with other cytotoxic products, the dose should be reduced accordingly. Commonly used doses are shown in the table above.

Impaired liver function

The major route of elimination of epirubicin is the hepatobiliary system. In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:

Serum Bilirubin	AST*	Dose Reduction
1.4 – 3 mg/100 ml		50%
> 3 mg/100 ml	> 4 times upper normal limit	75%

*AST – aspartate aminotransferase

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. Lower starting doses should be considered in patients with severe renal impairment (serum creatinine >450µmol/l).

Intravesical administration

Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations.

For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at the same dose.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

Dose Epirubicin required	Volume of 2 mg/ml epirubicin injection	Volume of diluent sterile water for injection or 0.9% sterile saline	Total volume for bladder installation
50 mg	25 ml	25 ml	50 ml

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 urine 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 by an appropriately qualified individual.

8. PATIENT INFORMATION LEAFLET (PIL)

PIL mock-up has been supplied and is satisfactory.

9. TECHNICAL LEAFLET

The technical leaflet is satisfactory.

10. LABELLING

Label mock-ups were supplied and are satisfactory.

11. APPLICATION FORM (MAA)

The MAA is medically satisfactory.

12. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory.

13. DISCUSSION

The absence of clinical data is satisfactory.

MEDICAL CONCLUSION

A marketing authorisation may be granted for this preparation.

5. OVERALL CONCLUSION

QUALITY

The important quality characteristics of Epirubicin Hydrochloride 2mg/ml Solution for Injection/Intravesical Use 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 an application of this type.

EFFICACY

Epirubicin is a well-known cytotoxic agent and has been used for many years to produce responses in a wide range of neoplastic conditions. The applicant has demonstrated essential similarity to the originator product, Pharmorubicin 2mg/ml Solution for injection.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with epirubicin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.