Safeguarding public health

MHRA

# Public Assessment Report

# Mutual Recognition Procedure

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

**MRP no: UK/H/844/01**
**UK licence no: PL 04515/0158**

**Applicant: Mayne Pharma Plc**

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

## LAY SUMMARY

Austria, Belgium, Cyprus, Denmark, Finland, Germany, Greece, Italy, Latvia, Lithuania, Luxembourg, Portugal and Spain today approved Mayne Pharma Plc Marketing Authorisations (licences) for the medicinal products Epirubicin Hydrochloride 2mg/ml Solution for Injection/Intravesical Use (PL 04515/0158) following acceptance of the UK marketing authorisation. These are prescription-only medicines (POM) used in the treatment of cancer of the breast, cancer of the stomach, advanced ovarian cancer, lung cancer, 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 approved.

# TABLE OF CONTENTS

# Module 1

| | |
|---|---|
| **Product Name** | Epirubicin Hydrochloride 2 mg/ml Solution for Injection/Intravesical Use |
| **Type of Application** | Abridged<br>Initial application<br>Generic, Article 10.1 [formerly 10.1(a)(iii)]<br>Chemical substance<br>Prescription only |
| **Active Substance** | Epirubicin Hydrochloride |
| **Form** | Solution for Injection/Intravesical Use |
| **Strength** | 2mg/ml |
| **MA Holder** | Mayne Pharma Plc |
| **RMS** | United Kingdom |
| **CMS** | Austria, Belgium, Cyprus, Denmark, Finland, Germany, Greece, Italy, Latvia, Lithuania, Luxembourg, Portugal and Spain |
| **Procedure Number** | UK/H/844/01 |
| **Timetable** | Day 90 23/02/2006 |

# Module 2

## SUMMARY OF PRODUCT CHARACTERISTICS

**1. NAME OF THE MEDICINAL PRODUCT**
Epirubicin Hydrochloride 2 mg/ml Injection

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
Epirubicin Hydrochloride 2 mg/ml
For a full list of excipients, see section 6.1

**3. PHARMACEUTICAL FORM**
Solution for Injection

A clear red solution.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**
Epirubicin is used in the treatment of a range of neoplastic conditions including;
- Carcinoma of the breast
- Advanced ovarian cancer
- Gastric cancer
- Small cell lung cancer

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of;
- Papillary transitional cell carcinoma of the bladder
- Carcinoma-in-situ
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

**4.2 Posology and method of administration**
Epirubicin is for intravenous or intravesical use only.

The safety and efficacy of epirubicin in children has not been established.

Intravenous administration
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). In case of extravasation, administration should be stopped immediately.

*Conventional dose*
When epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m$^2$ 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 haematological status and bone marrow function.

If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

*High dose*
Epirubicin as a single agent for the high dose treatment of lung cancer should be administered according to the following regimens:
Small cell lung cancer (previously untreated): 120 mg/m$^2$ day 1, every 3 weeks.

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

*Breast Cancer*
In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m$^2$ (as a single dose on day 1) to 120 mg/m$^2$ (in two divided doses on

days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

Lower doses (60-75 mg/m$^2$ for conventional treatment and 105-120 mg/m$^2$ 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:

| | **Epirubicin Dose (mg/m$^2$)[a]** | |
|---|---|---|
| **Cancer Indication** | **Monotherapy** | **Combination Therapy** |
| Advanced ovarian cancer | 60–90 | 50–100 |
| Gastric cancer | 60–90 | 50 |
| SCLC | 120 | 120 |
| Bladder cancer | 50 mg/50 ml or 80 mg/50 ml (carcinoma in situ)<br>Prophylaxis:<br>50 mg/50 ml weekly for 4 weeks then monthly for 11 months | |

[a] Doses 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 | Dose Reduction |
|---|---|
| 24 - 51 μmol/l | 50% |
| > 51 μmol/l | 75% |

*Impaired renal function*
Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine >5 mg/dL.

Intravesical administration
Epirubicin can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations (see Section 4.3). Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence.

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:
8 weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water).

If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.

Carcinoma-in-situ: Up to 80 mg/50 ml (depending on individual tolerability of the patient)

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 | Volume of diluent sterile | Total volume for |
|---|---|---|---|

| | epirubicin injection | water for injection or 0.9% sterile saline | bladder installation |
|---|---|---|---|
| 30 mg | 15 ml | 35 ml | 50 ml |
| 50 mg | 25 ml | 25 ml | 50 ml |
| 80 mg | 40 ml | 10 ml | 50 ml |

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

**4.3 Contraindications**

Epirubicin is contraindicated in:

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

For intravesical administration, epirubicin is contraindication in:

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

**4.4 Special warnings and 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.

Epirubicin can have genotoxic effects. Therefore, male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to because of the possibility of infertility due to therapy with epirubicin.

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

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

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

During treatment with epirubicin, red blood cell, white blood cell, neutrophil and platelet counts should be carefully monitored both before and during each cycle of therapy. Leucopenia and neutropenia are usually transient with conventional and high-dose schedules reaching a nadir between the $10^{th}$ and $14^{th}$ day, values should return to normal by the $21^{st}$ day; they are more severe with high dose schedules. Thrombocytopenia (< 100,000 platelets/$mm^3$) is experienced in very few patients, even following high doses of epirubicin.

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

In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900-1000 mg/$m^2$ 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/m$^2$, there is evidence that cardiac toxicity rarely occurs. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart failure of the type described for other anthracyclines. In case of cardiac insufficiency, treatment with epirubicin should be discontinued.

Cardiomyopathy induced by anthracyclines is associated with 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. Electrocardiogram (ECG) changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity. The risk of serious cardiac impairment may be decreased through regular monitoring of left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The preferred method for repeated assessment of cardiac function is evaluation of LVEF measure by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increase cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict.

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. Hydration, urine alkalinisation and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumor-lysis syndrome.

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 and/or who are under medical treatment with potentially cardiotoxic medicinal products (see Section 4.5).

Before commencing therapy with epirubicin, and if possible during treatment, liver function should be evaluated (SGOT, SGT, alkaline phosphatase, bilirubin), (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**

It is not recommended that Epirubicin Hydrochloride 2 mg/ml Injection be mixed with other medicinal products. However, epirubicin can be used in combination with other anti-cancer agents.

Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon $\alpha_2$b, paclitaxel and quinine.
Dexverapamil may alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects.

Prior administration of higher doses (900 mg/m$^2$ and 1200 mg/m$^2$) of dexrazoxane may increase the systemic clearance of epirubicin and result in a decrease in AUC.

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

The co-administration of interferon $\alpha_2$b may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.

Paclitaxel may affect the pharmacokinetics of epirubicin and its metabolite, epirubicinol. In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin compared with after epirubicin.

One study has shown that paclitaxel clearance is reduced by epirubicin.

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

Cimetidine 400 mg b.i.d given prior to epirubicin 100 mg/m$^2$ 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.

Epirubicin used in combination with other cytotoxic agents may result in additive myelotoxicity.

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

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

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

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

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

**4.6 Pregnancy and lactation**

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

Breastfeeding must be discontinued before and during therapy with Epirubicin Hydrochloride 2 mg/ml Injection.

**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.

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

**4.8 Undesirable effects**

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

*Infections and infestations:*
Fever, infections, pneumonia, sepsis and septic shock may occur as a result of myelosuppression.

*Neoplasms benign, malignant and unspecified (including cysts and polyps):*

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

*Blood and the lymphatic system disorders*:
Myelosuppression (leucopenia, granulocytopenia, neutropenia, febrile neutropenia, thrombo-cytopenia, anaemia). Haemorrhage and tissue hypoxia (as a result of myelosuppression) may occur.

High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and has caused adverse events which are no different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/$mm^3$ 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*:
Common: Allergic reactions following intravesical administration.
Uncommon: Sensitivity to light or hypersensitivity in the case of radiotherapy ("recall phenomenon").
Rare: Anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills).

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

*Vascular disorders*:
Uncommon: Thrombophlebitis
Coincidental cases of thromboembolic events (including pulmonary embolism [in isolated cases with fatal outcome]) have occurred.

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

*Skin and subcutaneous tissue disorders*:
Very common: Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.
Common: Hot flushes
Uncommon: Hyperpigmentation of skin and nails. Skin reddening.
Rare: Urticaria.

*General disorders and administration site conditions*:
Common: Mucositis – may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, ulceration and bleeding, mainly along the side of the tongue and the sublingual mucosa.
Common: Redness along the infusion vein. Local phlebitis, phlebosclerosis. Local pain and tissue necrosis (following accidental paravenous injection) may occur.
Uncommon: Headache
Rare: Fever, chills, dizziness, amenorrhea, azoospermia, hyperuricaemia (as a result of rapid lysis of neoplastic cells). Hyperpyrexia, malaise, weakness and increased transaminase levels have also been reported.

*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 antibiotics, blood transfusion and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to 6 months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines. Epirubicin is not dialyzable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent. ATC code: L01D B03

Epirubicin is a cytotoxic active antibiotic from the anthracycline group.

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 $mg/m^2$ of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Between 60 and 120 $mg/m^2$ there is an extensive linear pharmacokinetic, 150 $mg/m^2$ is at the margin of dose linearity. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

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

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

Following repeated dosing with epirubicin, the target organs in rat, rabbit and dog were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the rat, rabbit and dog.

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

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

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium Chloride
Water for Injections
Hydrochloric acid for pH adjustment

### 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 room temperature or for 28 days at 2-8ºC 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 8ºC.

**6.4 Special precautions for storage**

Store at 2°C – 8°C (in a refrigerator),
Keep the container in the outer carton in order to protect from light.

**6.5 Nature and contents of container**

Epirubicin Hydrochloride 2 mg/ml Injection is supplied in clear, ONCO-TAIN® vials containing 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 Instructions for use, handling and 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 04515/0158

**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

**This leaflet contains important information about your medicine; read it carefully.**
Keep this leaflet; you may want to read it again.
If you have any questions or are not sure about anything, 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 Injection

In this leaflet:



### 1. What Epirubicin Hydrochloride 2 mg/ml Injection is and what it is used for

Epirubicin Hydrochloride Injection is an anti-cancer medicine. Treatment with an anti-cancer medicine is sometimes called cancer chemotherapy.

Epirubicin hydrochloride is used in the treatment of;

- Breast cancer
- Advanced ovarian cancer
- Stomach cancer
- Lung cancer.

Epirubicin is also used to help prevent recurrence of bladder cancer after surgery.

### 2. Before you use Epirubicin Hydrochloride Injection

**Epirubicin Hydrochloride Injection should not be used:**

- if you have shown signs of hypersensitivity (severe allergy) to epirubicin hydrochloride or similar medicines on previous occasions
- 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 (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 pregnant or breastfeeding
- if you have a severe infection

When administered intravesically (directly into the bladder), Epirubicin should not be used if:

- the cancer has penetrated the bladder wall
- if you have an infection in your urine
- you have pain or inflammation in your bladder
- your doctor has problems inserting a catheter (tube) into your bladder
- there is a large volume of urine left in your bladder after you attempt to empty it.

**Special care will be taken:**

- to ensure the number of cells in your blood does not drop too low. Your doctor will regularly check this.
- if you are experiencing severe inflammation or ulcers in your mouth
- to check the level of uric acid in your blood. Your doctor will check this.
- if you have liver disease
- to ensure your heart is working properly. Your doctor will regularly check this.
- if you have received or are receiving radiotherapy to the chest area.
- if you are planning to start a family, whether you are male or female
- if you are taking any of the following medicines;
  other medicines that may affect your heart and/or liver
  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)
  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 ones that are not prescribed for you.

**Pregnancy and breast-feeding**

Both men and women should use effective contraception during treatment with epirubicin and for 6 months after treatment with epirubicin has finished.
You must not use epirubicin if you are breastfeeding.

**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 Injection

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 may be given as an injection into a vein over 3-5 minutes. It may also be diluted with glucose (sugar solution) or sodium chloride (salt water) before it is infused slowly, usually via a drip into a vein over 30 minutes. You may be given another dose of this medicine in 3 weeks.

By being put into the bladder (intravesical administration)

The medicine may be given directly into the bladder using a catheter. If this route is used, you should not drink any fluids for 12 hours before treatment so that your urine will not dilute the drug too much. The solution should be kept in your bladder for 1 hour after instillation. You will be rotated occasionally to ensure even exposure of all parts of the bladder to the drug.

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

While you are receiving epirubicin your doctor will 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 injection has been added to a bag of fluid for injection, or for administration to the bladder, it should be labelled with the strength of the drug, volume and the time after which it should not be used.

As this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too little or too much, however, tell your doctor or pharmacist if you have any concerns.

## 4. Possible Side Effects

Like all medicines, epirubicin can have side effects.

**If any of the following happen when epirubicin is given by infusion into a vein, tell your doctor immediately:**

- if there is any redness, pain or swelling at the injection site
- you have symptoms of heart problems such as chest pain, shortness of breath, swelling of your ankles (these effects may occur up to several weeks after finishing treatment with epirubicin)
- if you have a severe allergic reaction, symptoms include faintness, skin rash, itching, swelling of the face and difficulty in breathing or wheeze. In some cases collapse may occur.

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

Other side effects may also be noticed after infusion of epirubicin into a vein.

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

- feeling or being sick
- swelling and/or pain or dark areas (pigmentation) in your mouth
- ulcers and/or bleeding involving the lips and/or tongue and/or under the tongue
- pain when passing urine after instillation into the bladder, and/or blood in the urine
- loss of hair
- reduced growth of beard hair
- diarrhoea
- fever and/or chills (rarely seen) or symptoms of an infection
- hives (urticaria) (rarely seen)
- cough or symptoms of a chest infection
- feeling very dry or thirsty (dehydration)
- bruising or bleeding
- eye infections
- loss of appetite
- stomach pains
- hot flushes
- early menopause
- reddening along the vein used for the injection
- weakness or malaise

- dizziness
- headache
- reduced or absent sperm in the semen.

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

Epirubicin may also affect your heart function, liver function and the number of cells in your blood. Your doctor will monitor such effects with regular heart and blood tests.

If epirubicin is injected directly into the bladder (intravesically) you may experience pain or difficulty when passing urine. Blood may also be seen in your urine. If you notice either of these side effects you should inform your doctor.

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

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

## 5. How to store Epirubicin Hydrochloride Injection

Keep out of the reach and sight of children.

The vials will be stored at 2-8°C (in the refrigerator).

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

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

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

## 6. Further information

- The active substance is epirubicin hydrochloride
- The other ingredients are sodium chloride, water for injections and hydrochloric acid used as a pH adjuster.

Epirubicin Hydrochloride is in the form of a solution for injection.

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

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

The vials are available in single packs of 5ml, 25ml, 50ml or 100ml.

The marketing authorisation holder and company responsible for batch release in the EU is Mayne Pharma Plc, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, United Kingdom.

The manufacturer is Mayne Pharma Pty Ltd, Lexia Place, Mulgrave, Victoria 3170, Australia.

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria – Epirubicinhydrochlorid Mayne 2 mg/ml Injektionslösung
Belgium – Epirubicin Hydrochloride Mayne 2 mg/ml
Cyprus – Mayne Epirubicin Hydrochloride
Denmark – Epirubicin Mayne
Finland – Epirubicin Mayne
Germany – Epirubicinhydrochlorid Mayne 2 mg/ml Injektionslösung
Greece – Epirubicin Hydrochloride 2 mg/ml Injection
Italy – Epirubicina cloridrato Mayne 2 mg/ml soluzione iniettabile
Latvia – Epirubicin Mayne
Lithuania – Epirubicin Mayne
Luxembourg – Epirubicin Mayne 2 mg/ml
Portugal – Epirrubicina Mayne 2 mg/ml solução injectável
Spain – Epirubicina Mayne 2 mg/ml solución inyectable

**This leaflet was last approved in** 02/2006

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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 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 injection 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 room temperature 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.

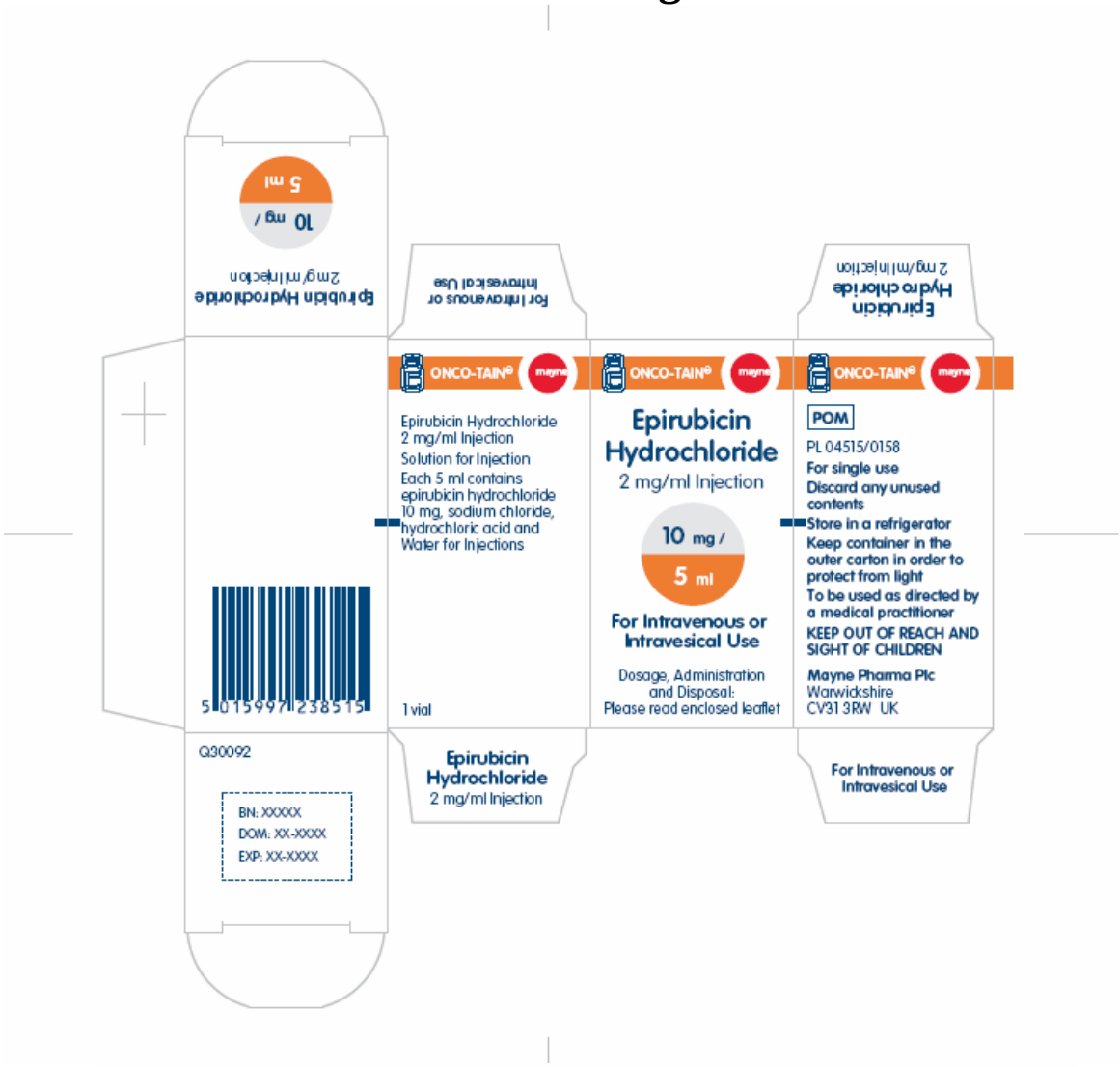
**Marketing Authorisation Holder**

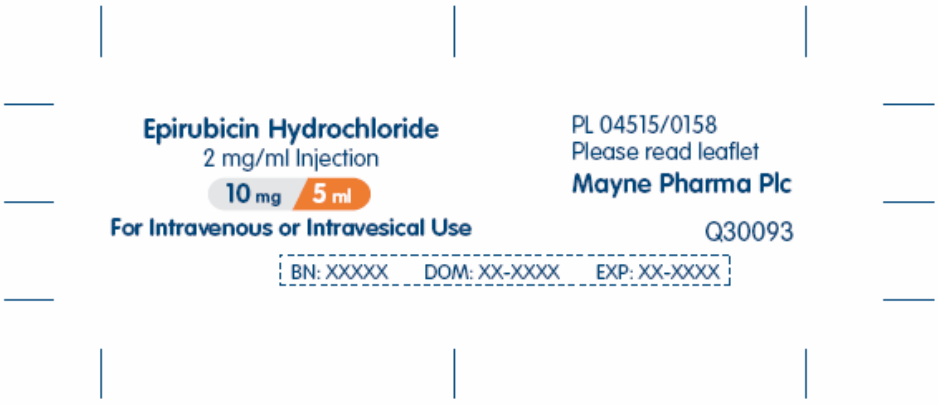
Mayne Pharma Plc
Warwickshire, CV31 3RW
UK

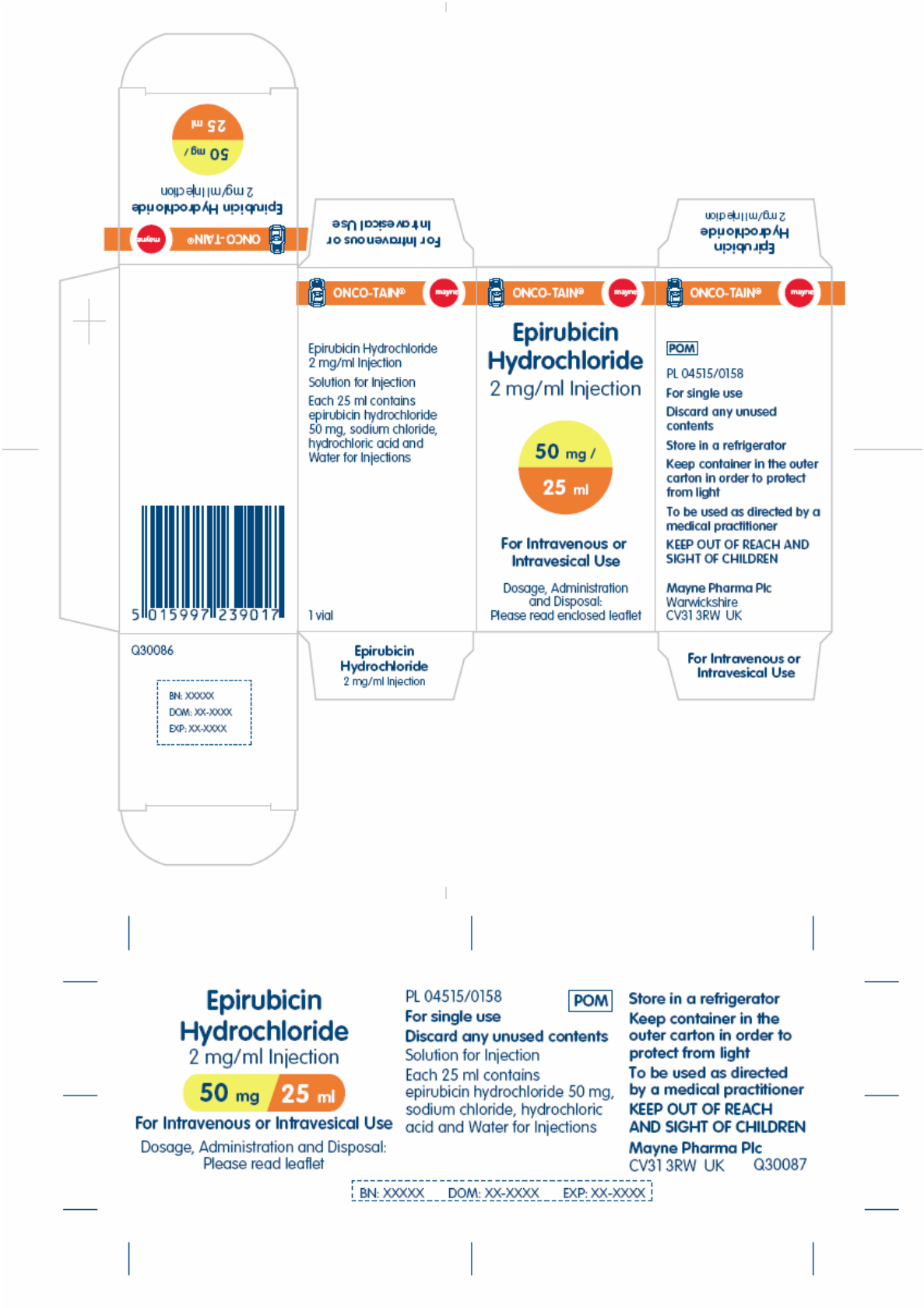
This leaflet was last approved in 02/2006

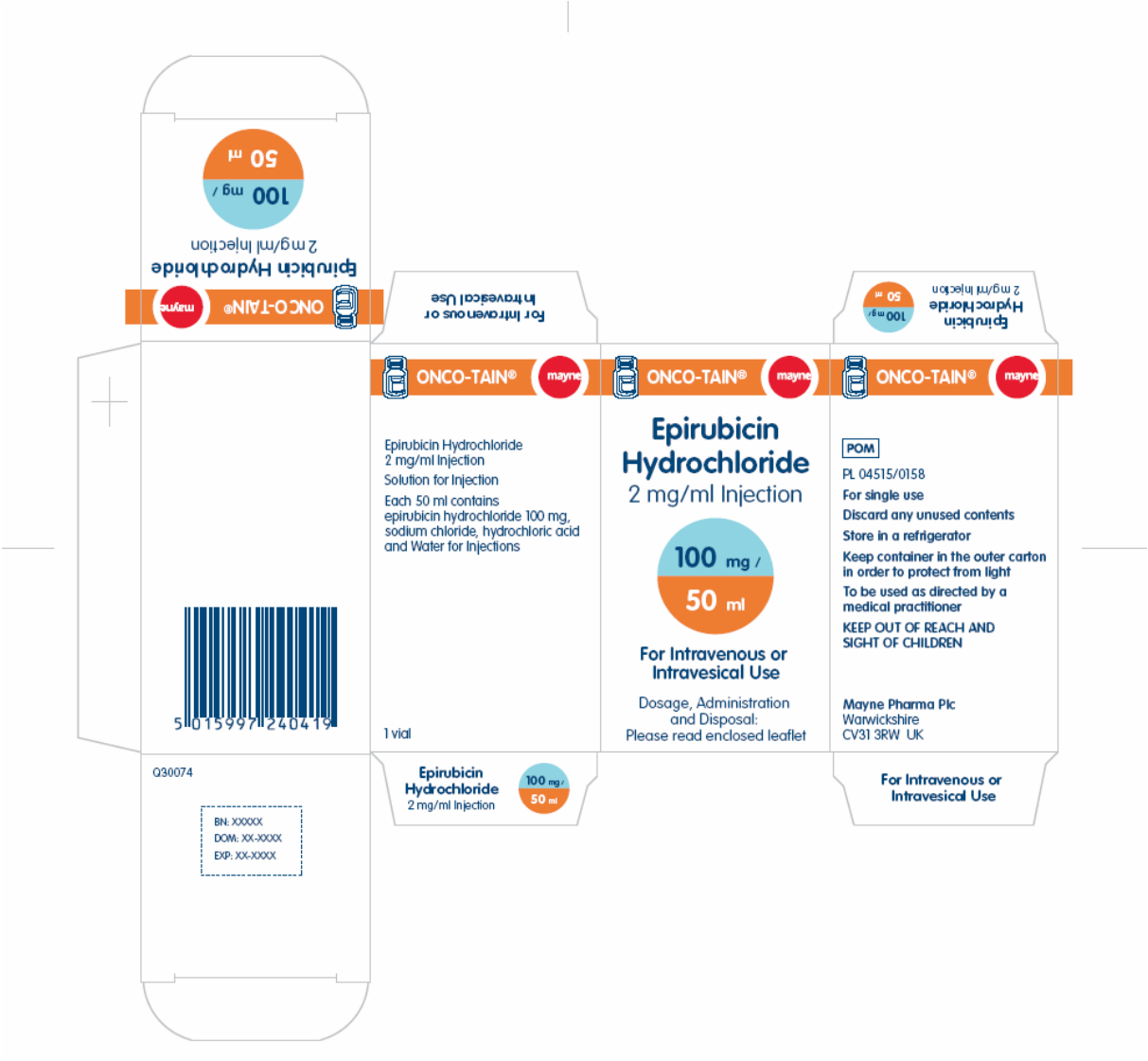
# Module 4

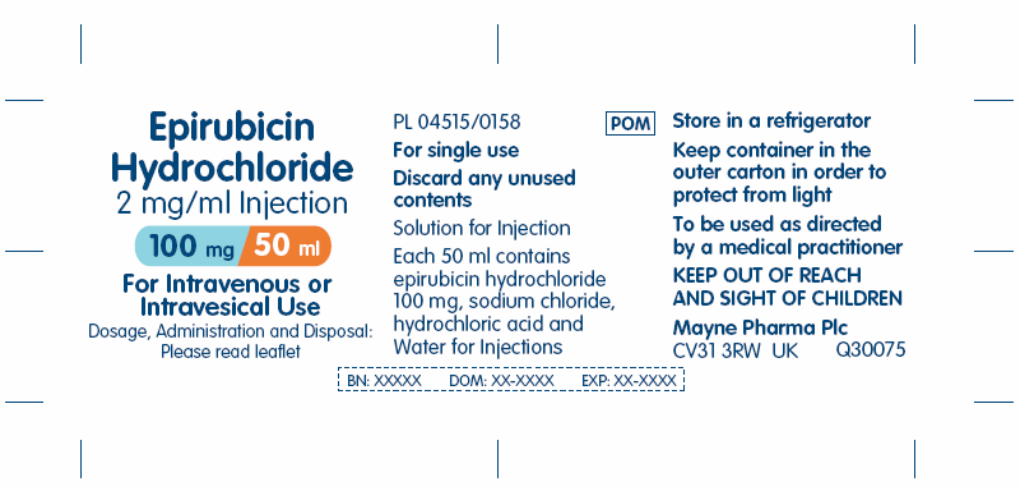
# Labelling

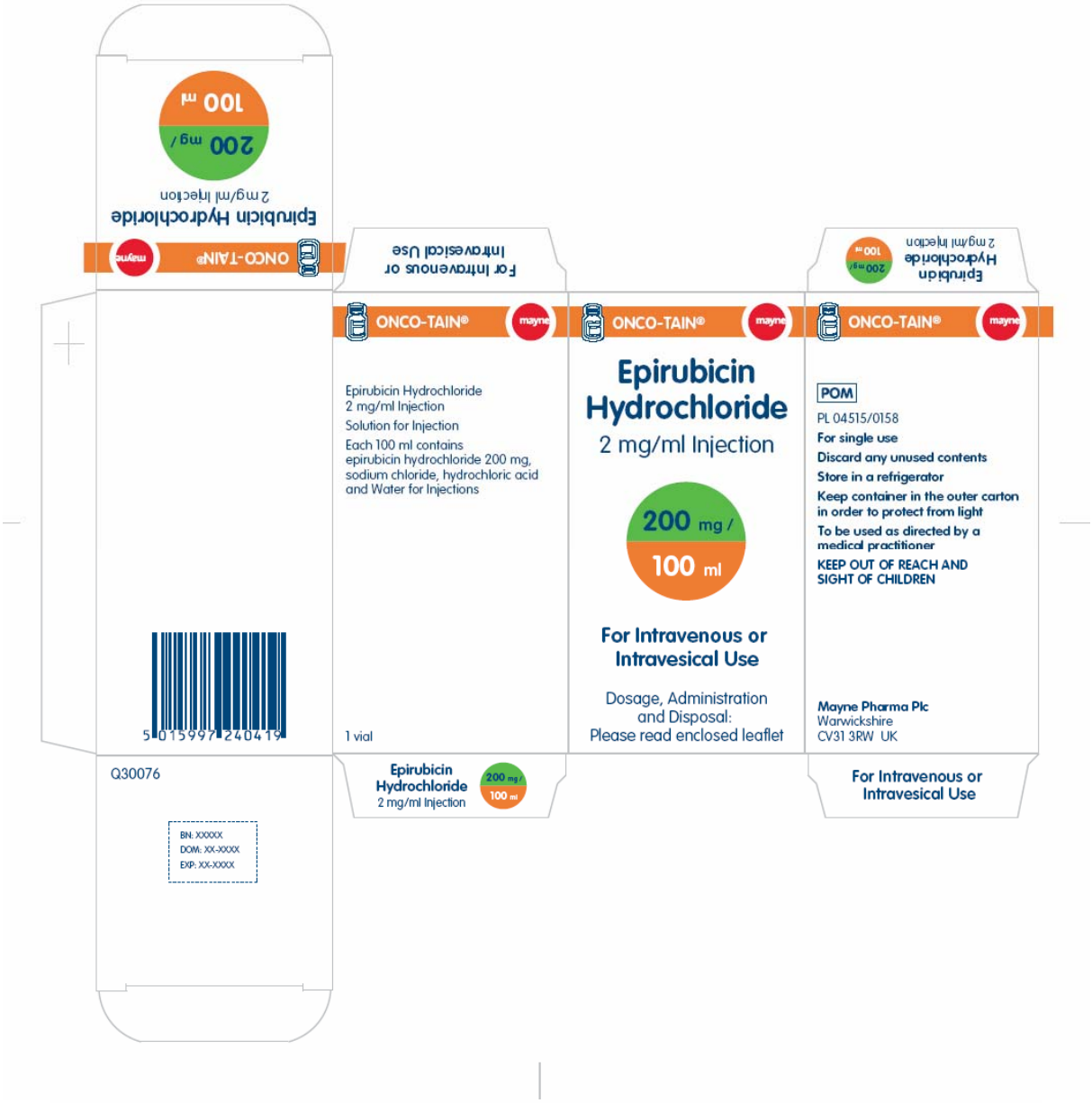


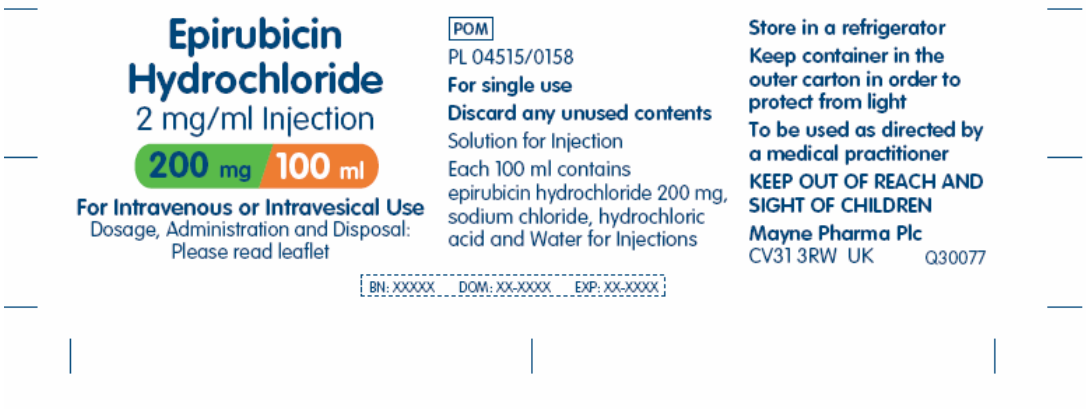




ONCO-TAIN®
Epirubicin Hydrochloride
2 mg/ml Injection
50 mg / 25 ml
For Intravenous or Intravesical Use
Epirubicin Hydrochloride
2 mg/ml Injection
Solution for Injection
Each 25 ml contains epirubicin hydrochloride 50 mg, sodium chloride, hydrochloric acid and Water for Injections
1 vial
POM
PL 04515/0158
For single use
Discard any unused contents
Store in a refrigerator
Keep container in the outer carton in order to protect from light
To be used as directed by a medical practitioner
KEEP OUT OF REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Warwickshire
CV31 3RW UK
Dosage, Administration and Disposal:
Please read enclosed leaflet
5 015997 239017
Q30086
BN: XXXXX
DOM: XX-XXXX
EXP: XX-XXXX
Q30087


ONCO-TAIN®
mayne
Epirubicin Hydrochloride
2 mg/ml Injection
100 mg / 50 ml
For Intravenous or Intravesical Use
Epirubicin Hydrochloride
2 mg/ml Injection
Solution for Injection
Each 50 ml contains epirubicin hydrochloride 100 mg, sodium chloride, hydrochloric acid and Water for Injections
1 vial
Dosage, Administration and Disposal:
Please read enclosed leaflet
POM
PL 04515/0158
For single use
Discard any unused contents
Store in a refrigerator
Keep container in the outer carton in order to protect from light
To be used as directed by a medical practitioner
KEEP OUT OF REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Warwickshire
CV31 3RW UK
5 015997 240419
Q30074
BN: XXXXX
DOM: XX-XXXX
EXP: XX-XXXX


Epirubicin Hydrochloride
2 mg/ml Injection
100 mg 50 ml
For Intravenous or Intravesical Use
Dosage, Administration and Disposal:
Please read leaflet
PL 04515/0158
For single use
Discard any unused contents
Solution for Injection
Each 50 ml contains epirubicin hydrochloride 100 mg, sodium chloride, hydrochloric acid and Water for Injections
POM
Store in a refrigerator
Keep container in the outer carton in order to protect from light
To be used as directed by a medical practitioner
KEEP OUT OF REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
CV31 3RW UK
Q30075
BN: XXXXX DOM: XX-XXXX EXP: XX-XXXX


ONCO-TAIN®
mayne
Epirubicin Hydrochloride
2 mg/ml Injection
200 mg / 100 ml
For Intravenous or Intravesical Use
Epirubicin Hydrochloride
2 mg/ml Injection
Solution for Injection
Each 100 ml contains epirubicin hydrochloride 200 mg, sodium chloride, hydrochloric acid and Water for Injections
1 vial
Dosage, Administration and Disposal:
Please read enclosed leaflet
POM
PL 04515/0158
For single use
Discard any unused contents
Store in a refrigerator
Keep container in the outer carton in order to protect from light
To be used as directed by a medical practitioner
KEEP OUT OF REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Warwickshire
CV31 3RW UK
5 015997 240419
Q30076
BN: XXXXX
DOM: XX-XXXX
EXP: XX-XXXX


Epirubicin Hydrochloride
2 mg/ml Injection
200 mg 100 ml
For Intravenous or Intravesical Use
Dosage, Administration and Disposal:
Please read leaflet
POM
PL 04515/0158
For single use
Discard any unused contents
Solution for Injection
Each 100 ml contains epirubicin hydrochloride 200 mg, sodium chloride, hydrochloric acid and Water for Injections
Store in a refrigerator
Keep container in the outer carton in order to protect from light
To be used as directed by a medical practitioner
KEEP OUT OF REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
CV31 3RW UK
Q30077
BN: XXXXX DOM: XX-XXXX EXP: XX-XXXX

# 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:

**Intravenously**

- Carcinoma of the breast
- Advanced ovarian cancer
- Gastric cancer
- Small cell lung cancer

**Intravesically**

- Papillary transitional cell carcinoma of the bladder
- Carcinoma-in-situ
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

Marketing Authorisations were approved in Austria, Belgium, Cyprus, Denmark, Finland, Germany, Greece, Italy, Latvia, Lithuania, Luxembourg, Portugal and Spain. The product names in these CMS's are:

**Austria:** Epirubicin hydrochlorid Mayne 2 mg/ml Injektionslösung
**Belgium:** Epirubicin Mayne 2 mg/ml
**Cyprus:** Mayne Epirubicin Hydrochloride
**Denmark:** Epirubicin Mayne
**Finland:** Epirubicin Mayne
**Germany:** Epirubicin hydrochlorid Mayne 2 mg/ml Injektionslösung
**Greece:** Epirubicin Mayne
**Italy:** Epirubicina cloridrato Mayne 2 mg/ml iniettabile
**Latvia:** Epirubicin Mayne
**Lithuania:** Epirubicin Mayne 2 mg/ml Injekcinis Tirpalas
**Luxembourg:** Epirubicin Mayne 2 mg/ml
**Portugal:** Epirrubicina Mayne 2 mg/ml Concentrado para solução injectável
**Spain:** Epirubicina Mayne 2 mg/ml solución inyectable
**United Kingdom:** Epirubicin Hydrochloride 2 mg/ml Injection

**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.

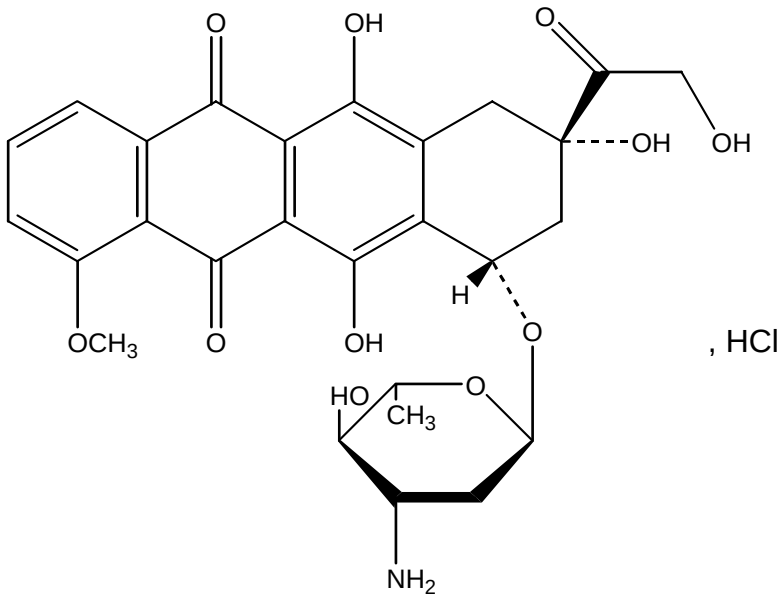
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has 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 $4^{o}C \pm 2^{o}C$ and $15^{o}C \pm 2^{o}C$.

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 $4^{o}C$, 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$^{o}$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* $4^{th}$ 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$^{o}$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$^{o}$C/60%RH. Assay, pH, related substances were tested for at all times. Testing at 15$^{o}$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$^{o}$C met the specification. Storage at 15$^{o}$C showed batches met specification, but impurities were increasing. Batches stored at 25$^{o}$C showed degradation.

The quality summary report states that the data support a 24 month shelf-life at 2-8$^{o}$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$^{o}$C and 15$^{o}$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$\pm$2$^{o}$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$^{o}$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$^{o}$C in the absence of light and 25$\pm$2$^{o}$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

Epirubicin is used in the treatment of a range of neoplastic conditions including:

- Carcinoma of the breast
- Advanced ovarian cancer
- Gastric cancer
- Small cell lung cancer

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of:

- Papillary transitional cell carcinoma of the bladder
- Carcinoma-in-situ
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

## 3. DOSE & DOSE SCHEDULE

Epirubicin is for intravenous or intravesical use only.

The safety and efficacy of epirubicin in children has not been established.

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). In case of extravasation, administration should be stopped immediately.

*Conventional dose*

When epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m$^2$ 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 haematological status and bone marrow function.

If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

*High dose*

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

Small cell lung cancer (previously untreated): 120 mg/m$^2$ day 1, every 3 weeks.

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

*Breast Cancer*

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m$^2$ (as a single dose on day 1) to 120 mg/m$^2$ (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

Lower doses (60-75 mg/m$^2$ for conventional treatment and 105-120 mg/m$^2$ 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** |
| Advanced ovarian cancer | 60–90 | 50–100 |
| Gastric cancer | 60–90 | 50 |
| SCLC | 120 | 120 |
| Bladder cancer | 50 mg/50 ml or 80 mg/50 ml (carcinoma in situ)<br>Prophylaxis:<br>50 mg/50 ml weekly for 4 weeks then monthly for 11 months | |

[a] Doses 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 | Dose Reduction |
|---|---|
| 24 - 51 μmol/l | 50% |
| > 51 μmol/l | 75% |

*Impaired renal function*
Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine >5 mg/dL.

Intravesical administration
Epirubicin can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations (see Section 4.3). Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence.

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:
8 weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water).

If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.

Carcinoma-in-situ: Up to 80 mg/50 ml (depending on individual tolerability of the patient)

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 |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 30 mg | 15 ml | 35 ml | 50 ml |
| 50 mg | 25 ml | 25 ml | 50 ml |
| 80 mg | 40 ml | 10 ml | 50 ml |

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