CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Epirubicine hydrochloride 2 mg/ml, solution for injection or infusion Pharmachemie B.V., the Netherlands

epirubicin hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1250/001/DC
Registration number in the Netherlands: RVG 101490

27 August 2009

Pharmacotherapeutic group:	anthracyclines and related substances
ATC code:	L01DB03
Route of administration:	intravenous or intravesical use
Therapeutic indication:	breast carcinoma; gastric carcinoma; papillary transitional cell carcinoma of the bladder; carcinoma in-situ; intravesical prophylaxis of recurrence of superficial bladder carcinoma following transurethral resection.
Prescription status:	prescription only
Date of authorisation in NL:	17 February 2009
Concerned Member States:	Decentralised procedure with AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Epirubicine hydrochloride 2 mg/ml, solution for injection or infusion, from Pharmachemie B.V.. The date of authorisation was on 17 February in the Netherlands.

In European countries epirubicin hydrochloride, as generic substance, has obtained marketing authorization for a diversity of therapeutic indications. The therapeutic indications approved for this oncolytic substance vary per application (of the innovator and generics) and also per country. The MAH claimed several indications that could not be granted. Refer to section II.3 for a discussion of these indications.

The product is indicated for the treatment of a range of neoplastic conditions including:

- Breast carcinoma
- Gastric carcinoma

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 recurrence of superficial bladder carcinoma following transurethral resection.

Epirubicine hydrochloride 2 mg/ml can be used in polychemotherapy schedules.

A comprehensive description of the indications and posology is given in the SPC.

Epirubicin belongs to the group of anthracyclins. The working mechanism of epirubicin depends on its ability to form complexes with DNA. Experimental studies with cell cultures have shown that epirubicin rapidly penetrates the cell and is recovered in the nucleus where it inhibits the nucleic acid synthesis and the mitosis. The activity of epirubicin was established on many experimental tumours, amongst which leucaemias L1210 and P388, the sarcoma SA 180 (solid and ascetic form), the B16 melanoma, the breast carcinoma, the lung carcinoma of Lewis and the colon carcinoma 38, furthermore an effect was also shown on human tumours that were transplanted in athymic nude mice (melanoma and mammary, lung, prostate and ovarian carcinoma).

Epirubicin is not orally absorbed. After iv administration, highest concentrations are found in the liver, spleen, kidney, and the small intestines. It is metabolized mainly in the liver, but also in other tissues, into epirubicinol which is also active. Biliary excretion is the major route of elimination (40%). The benefits of anthracyclines (doxorubicin, daunorubicin, epirubicin and idarubicin) in the treatment of malignant disease are known for decades. However, a major limitation to the use of anthracyclinesis cardiotoxicity that limits its use from a cumulative dose, irrespective of any favourable effect. Therefore the use is mitigated after heart function compromising radiotherapy or – chemotherapy. Contraidications are founded in (pre existing) cardiovascular disease and hepatic dysfunction.
During the eighties attempts to modify the ‘core’ anthracycline molecule in order to minimize anthracycline induced cardiotoxicity *without* decreasing efficacy have not been very successful: Although epirubicin is less toxic than doxorubicin, compared to doxorubicin it is however also less biologically active.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Farmorubicin 2 mg/ml injektionsvätska which has been registered in Sweden by Pfizer AB since 1989. In the Netherlands, Farmorubicine R.T.U. 2 mg/ml (NL RVG 14943), oplossing voor intraveneuze infusie has been registered since 1992. The differences of the product at issue compared to the reference medicinal product are a change in therapeutic indications and a change in route of administration. In addition, reference is made to Farmorubicin authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Epirubicine hydrochloride 2 mg/ml is a product for parenteral use in an aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

General information
The active substance is epirubicin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is soluble in water and methanol, slightly soluble in ethanol an practically insoluble in acetone.
Epirubicin hydrochloride precipitates at the beginning as a crystal, incorporating the crystallization solvent. The crystalline elementary structure is well defined and characterized by univocal diffraction lines. The presence of the solvent ensures its crystallographic stability. During the drying, the crystallization solvent is removed from the crystalling element, leaving an amorphous-like powder with some traces of the original crystalline structure.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The MAH submitted a reaction scheme including the reagents and solvents as well as a summary of the two step manufacturing process. A detailed description of the manufacturing process was submitted. Control of materials, critical steps and intermediates as well as the process validation and manufacturing process development were included.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur. with additional requirements for residual solvents and microbiological quality. Acetone which is listed in the monograph is not used in the

manufacturing process and therefore not included in the specifications. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided by the ASMF-holder for four full scaled batches stored at 25°C/60% RH (six months) and 5°C±3°C (36 months). When stored at 5°C the water content demonstrates a maximum increase of 2.4% (from 1.3% to 3.7%) but remains within the specification. The other parameters do not change. For the batches stored at 25°C comparable results are obtained, however, the water content shows a more pronounced increase after 6 months of storage.
Based on the submitted stability data the re-test period of 12 months claimed by the MAH could be granted, when stored between 2-8°C in the original package.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Epirubicine hydrochloride 2 mg/ml contains as active substance 2 mg of epirubicin hydrochloride per millilitre, and is a clear red solution.

The solution for injection or infusion is packed in a colourless type I glass vial with a bromobutyl rubber cap, aluminium closing and snap-cap containing 5 ml, 10 ml, 25 ml, 75 ml and 100 ml of epirubicine hydrochloride as a sterile, preservative-free solution. No overage is applied.

The excipients are: sodium chloride, hydrochloric acid (for pH adjustment), water for injections
The excipients and packaging are usual for this type of dosage form. The excipients comply with the Ph.Eur. with additional specifications for sodium chloride concerning mesophilic count and for water for injections regarding silicates. These specifications are acceptable.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justistied and their functions explained. No clinical trials have been carried out since the solution is a generic product for parenteral infusion. The pharmaceutical development of the product has been adequately performed. Compatibility studies demonstrated compatibility with sodium chloride 0.9%, glucose 5% and water for injection in infusion bags.

Manufacturing process
Epirubicine HCl is dissolved in part of the water for injections under nitrogen purging. The solution of sodium chloride is added. Water for injections is added to reach the final weight and homogenized. The solution was filtered into a sterile collecting vessel. The sterilised vials are then aseptically filled with the solution under nitrogen overlay. The vials are closed with the sterilised stoppers and copped. The vials are washed and sleeved.
The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches. The MAH committed to provide validation data of two additional batches post authorisation.

Compatibility
Epirubicin HCl, solution for infusion 2 mg/ml will be injected into a running infusion and will be used for intravesical administration, therefore dilution studies have been performed. The drug product has been added to sodium chloride 0.9% and to glucose 5% infusion bags in concentrations of 0.6 and 1.6 mg/ml. It has also been diluted with sodium chloride 0.9%, with glucose 5% and with water for injections in 5 ml polypropyleen syringes in the same concentrations. The infusion bags as well as the syringes were all stored at two temperatures (2-8°C and 15-25°C) and sampled during four weeks. It was tested on

appearance, pH, particulate matter, related substances and assay. No differences were observed during the four weeks. Compatibility with polypropylene syringes and Viaflex® infusion bags has been demonstrated. Argumentation is given that the product is compatible with the regular lining of infusion systems.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, closure intergrity, extractable volume, particulate contamination (visible and sub-visible), pH, related substances, sterility and endotoxins. The release and shelf-life specifications are overall the same with the exception of the limitations on related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on ten full scaled batches, demonstrating compliance with the release specification. The MAH committed to perform compatibility and dilution studies in PVC free bags on samples near the expiration date and submit the results to the RMS and all CMS countries. The MAH also committed to place the highest size batches under stability studies and provide real time data up to 24 months for reassessment of the assay lower end limit 92.5%. If real time results are within 95-105%, the MAH committed to provide readjustment of the shelf-life specification by a variation.

Container closure system
As a primary container colourless glass vials of hydrolytic class I were chosen. The quality of the material meets the specifications of the Ph.Eur. The sizes of the vials for individual packages are 10.0 ml, 13.5 ml, 36.0 ml and 119.0 ml. The used bromobutyl rubber stoppers comply with the Ph.Eur.

Stability tests on the finished product
Stability data on the product has been provided for two production scale batches of each volume stored at 5°C (24 months) and 25°C± 2°C/ 60% RH ± 5% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in colourless glass vials, hydrolytic class I, with bromobutyl rubber cap and aluminium fixing shell.
In all batches a slight increase in assay is observed versus a slight decrease in total related substances at 5°C over a 24 month period. An increase of particulate contamination was also observed. Under accelerated conditions a significant decrease in assay within three months was observed. A shelf life was granted of 2 years. The labelled storage conditions are *'Store in the refrigerator (2-8°C)'*, *'Store and transport refrigerated'* and *'Do not freeze'*.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of epirubicine hydrochloride are well known. As epirubicine hydrochloride is a widely used, well-known active substance, no further studies are required and the applicant provides non. A non-clinical overview is based on literature review only is appropriate.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of epirubicin hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Epirubicine hydrochloride is a well-known active substance with established efficacy and tolerability.

Epirubicine hydrochloride 2 mg/ml, solution for injection or infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Epirubicine hydrochloride 2 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Clinical efficacy

In European countries epirubicin hydrochloride, as generic substance, has obtained marketing authorization for a diversity of therapeutic indications. The therapeutic indications approved for this oncolytic substance vary per application (of the innovator and generics) and also per country.

For Epirubicine hydrochloride 2 mg/ml, the MAH requested a marketing authorisation for the following indications:

- *leukaemia (acute lymphatic leukaemia, acute non-lymphatic leukaemia)*
- *malignant lymphoma (Hodgkin and non-Hodgkin lymphoma)*
- *mammary carcinoma*
- *soft tissue sarcoma*
- *ovarian carcinoma*
- *stomach carcinoma*
- *lung carcinoma*
- *colorectal carcinoma*
- *multiple myeloma*
- *Intravesical administration has appeared beneficial for the treatment of superficial bladder carcinoma and prophylaxis of recurrrence after transurethral resection.*

Epirubicin hydrochloride 2 mg/ml can be used in polychemotherapy schedules.

In support of the proposed indications the MAH submitted a clinical overview, summarizing the clinical results obtained with epirubicin in various neoplastic conditions since the product was marketed.

All indications sought for epirubicin in this application are commentated upon in view of the therapeutic indications for Epirubicin hydrochloride Mayne 2 mg/ml that were approved in 2006 following a MRP procedure UK/H/868/001 in Estonia, Norway, Sweden and the Netherlands (NL RVG 33726).

- Leukaemia: The usual remission induction regimens in acute myeloid leukemia (AML) encompass cytarabine, daunorubicin or idarubicin. Epirubicin is not considered a standard component in treatment regimen.
  In acute lymphatic leukemia (ALL) anthracyclins as daunorubicin, doxorubicin and zorubicin are applied in remission induction. However, epirubicin is currently not considered an standard. The indication was not supported by up to data scientific literature data. In view of the current standard therapy regimen for leukaemia's, and in line with the SPC of Epirubicin Mayne 2 mg/ml. Therefore the indication leukaemia's for epirubicin was considered **not** approvable.

- Malignant lymphoma:

- Hodgkin lymphoma
  Member states considered that 'favourable prognosis Hodgkin's disease' may not be founded robustly enough to justify this as an established indication, therefore it was decided to delete this indication. Furthermore, besides the fact that this indication for epirubicin is not generally accepted within the EU, to date there is no data to justify the use of epirubicin in the standard treatment modalities for this disease.
- Non-Hodgkin lymphoma (NHL)

Epirubicin is not a part of standard polychemotherapy regimens in non-Hodgkin lymphoma. Some reports suggest modest advantages for epirubicin containing regimen in the elderly with aggressive NHL (Sung et al. Br J Haematol 2006 134:45-53, Merli et al. Hematologica 2004 89:973-2224). Nevertheless, the indication non Hodgkin's lymphoma as such is not broadly supported by up to date literature. Therefore, in line with the SPC of Epirubicin Mayne 2 mg/ml, the indication NHL was considered **not** approvable.

- Mammary carcinoma/Breast cancer: The most widely used adjuvant regimens have been cyclophosphamide, methotrexate and 5-FU (CMF), anthracycline-based regimens, such as AC (doxorubicin plus cyclophosphamide) with or without a taxane, CAF (cyclophosphamide, doxorubicin, 5 FU), and FEC/ CEF (cyclophosphamide, epirubicin, and 5-FU), By now the advantage of using anthracycline-containing versus non-anthracycline (ie, CMF-type) regimens has been proven in comparative studies (See: Lancet, 2005, 365:1687). To date the use of epirubicin as part of polychemotherapy regimens is considered established therapy in breast cancer.

- Soft tissue sarcoma (STS): The highest response rates have been achieved observed with doxorubicin and ifosfamide-containing combinations, but the toxicity of such a combined approach is considerable. Also for this reason, two trials have directly compared epirubicin with single agent doxorubicin for STS. One EORTC trial randomly assigned 334 patients with untreated metastatic sarcoma to doxorubicin, or high dose epirubicin on one of two different schedules. The epirubicin schedule was worse (Nielsen et al. Br J Cancer 1998;78:1634). In an other report, also mentioned by the MAH in the Clinical Overview, 210 patients received either epirubicin or doxorubicin once every three weeks (Moouridsen HT et al. Euro J Cancer Clin Oncol 1987; 23: 1477). There was a slight trend toward a lower response rate with epirubicin (18 versus 25 percent), but duration of response and median survival were similar. To date, the standard therapy of STS does not encompass the application of epirubicine. Epirubicine hydrochloride Mayne 2 mg/ml is not authorised for the indication STS in NL and the indication is not supported by up to date scientific literature. Therefore, the indication STS was considered **not** approvable.

- Ovarian carcinoma: Since the adoption of the platinum-plus-taxane combination as the standard nearly worldwide, clinical trials have demonstrated increased toxic effects but no advantage of adding epirubicin to the carboplatin plus paclitaxel doublet (Kristensen et al. Int J Gynecol Cancer 2003, 13 (Suppl 2): 172-177). There may be a small role for epirubicin in salvage chemotherapeutic treatment (Zanaboni et al. Gynecol Oncol 1991, 43:24-28). Others also considered that addition of epirubicin to standard regimen (platin/taxane) did not improve survival or time to treatment failure in patients with advanced epithelial ovarian cancer (du Bois et al. J Clin Oncol 2006, 24:1127-1135), therefore, epirubicin cannot be recommended for clinical use in this population. Epirubicin hydrochloride Mayne 2 mg/ml is not authorised for the indication ovarian cancer in NL and the indication is not supported by up to date scientific literature. Therefore, the indication advanced ovarian cancer was **not** approved.

- Gastric carcinoma/stomach carcinoma: Currently the combination treatment with epirubicin, ciplatin and 5-FU (ECF) appears the most effective. In NL this regimen is considered the standard (palliative) treatment modality. Ample scientific information corroborates this strategy. Therefore, the indication gastric carcinoma was considered approvable.

- Small cell lung carcinoma (SCLC): To date the combination therapy with a platin compound with a (third generation) chemotherapeutic is the standard approach. The combination of cisplatin with etoposide is currently the preferred combination and CDDP/epirubicin can also be applied with comparable results (PFS, OS) albeit with slightly higher toxicity and lesser compliance (Artel Cortes et al. clin Lung Cancer 2004, 6:175-183). The combination of epirubicin plus cisplatin is not a standard regimen for the treatment of patients with SCLC. Therefore, the indication SCLC is considered **not** approvable.

- Colorectal carcinoma: Currently there are no standard treatment modalities that involve the application of epirubicin. Furthermore, the reference product has not been authorised for the indication colorectal

carcinoma in NL and also the indication is not supported by up to date scientific literature. Therefore, the indication colorectal cancer was considered not approvable.

- Bladder cancer:
  - Superficial bladder cancer: Epirubicin has been reported to be of value in the chemotherapeutic treatment of carcinoma in situ of bladder cancer (Oosterlink et al. J Urol 1993, 149:749-752), albeit that, despite improvement of recurrence rate and recurrence free survival, there seems a limited impact on overall survival (Oosterlinck et al. J Urol 1993, 149:749-752). Although the result obtained from BCG instillation in superficial bladder cancer are still superior to those from epirubicin, the application of epirubicin is currently considered an acceptable other treatment option (for those not suitable to receive live attenuated mycobacteria).
  - Profylaxis of recurrence of superficial bladder cancer: For prophylaxis of recurrences of primary superficial bladder cancer the instillation of single dose epirubicin seems effective, although no data on the risk on invasive disease and OS are known yet (Rajala et al. J Urol 2002 Sep; 168(3); 981-985.). Results have been confirmed by Liu et al (Cancer Invest 2006, 24:160-163). Earlier, others found that the application did not result in preventing tumour recurrence and, conversely, epirubicin may even promote tumourprogression in bladders with dysplastic mucosal changes (Igawa et al. Br J Urol 1996, 78: 662). This indication is included in the listing of therapeutical indications for Epirubicin Mayne 2 mg/ml, therefore the application for epirubicin in treatment and prophylaxis of superficial bladder cancer can be considered acceptable.

- Multiple Myeloma
  Although the introduction of several new components has constituted an important advance in the treatment of multiple myeloma (for instance bortezomib, lenalidomide), to date patient survival remains unsatisfactory. Therefore, many combinations of chemotherapeutic agents have been tried. Examples of antineoplastic agents are those from the M2 protocol (vincristine, carmustine (BCNU), melphalan, cyclophosphamide, and prednisone) and the ABCM regimen (adriamycin, BCNU, cyclophosphamide, and melphalan). According to current standards epirubicin does not constitute a useful tool in the systemic treatment of MM. Therefore, and also in line with the SPC of Epirubicin Mayne 2 mg/ml, the indication MM was considered **not** approvable.

At the end of the MRP, the following indications were approved by all member states:
- Breast carcinoma
- Gastric carcinoma

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

However, the MAH was requested to submit a type II variation within 2 months after finalisation of the DCP in order to justify the intravesical administration of epirubicin (in the treatment of: Papillary transitional cell carcinoma of the bladder, carcinoma in situ and intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection) by providing relevant data. The MAH committed not to place the product on the market in France until finalisation of the type II variation indicated (NL/H/1250/001/II/001). On 27 January 2009 the MAH has submitted this type II variation, which was approved on 10 June 2009.

Risk management plan

Epirubicin was first approved in 1982, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of epirubicin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with the accepted wording in procedures UK/H/868/MR, PT/H/172/MR, DK/H/426/MR, DK/H/1124/DC, NL/H/1084/DC and UK/H/1123/DC.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.
The questionnaire consisted of 11 questions (all existing of two sub-questions) specific to Epirubicine hydrochloride 2 mg/ml solution for injection or infusion and the format of the package leaflet, and two questions to obtain general feedback on the user friendliness of the package leaflet. Adults of either sex were recruited. The demographics, e.g. sex, age, occupation and highest educational achievement, of the test population were provided. A first test was performed with 10 participants. The following areas for attention with regard to improving the patient information leaflet were identified during the study: sections “Do not use Epirubicine”, “Use in combination with other medicines”, and “Possible adverse events”. Several modifications were implemented. Based on the results of the second test round, the patient information leaflet’s readability was 91%. Following this round, the package leaflet was not adapted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Epirubicine hydrochloride 2 mg/ml solution for injection or infusion, is considered a hybrid of the reference medicinal product Farmorubicine R.T.U. 2 mg/ml, already marketed in different European countries, i.e. it satisfies the criteria of having the same qualitative and quantitative composition in terms of active ingredients with the reference medicinal product, but there are difference in therapeutic indications and in route of administration. Farmorubicine R.T.U. 2 mg/ml, oplossing voor intraveneuze infusie, is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are aqueous solutions intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other epirubicine hydrochloride containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Epirubicine hydrochloride 2 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 November 2008. Epirubicine hydrochloride 2 mg/ml was authorised in the Netherlands on 17 February 2009.

A European harmonised birth date has been allocated (28 June 1982) and subsequently the first data lock point for Epirubicin is June 2011. The first PSUR will cover the period from November 2008 to June 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 13 November 2013.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to provide validation data of two additional batches.
- The MAH committed to place the highest size batches under stability studies and provide real time data up to 24 months for reassessment of the assay lower end limit 92.5%. If real time results are within 95-105%, the MAH committed to provide readjustment of the shelf-life specification by a variation.
- The MAH committed to perform compatibility and dilution studies in PVC free bags on samples near the expiration date.

Clinical aspects

- The MAH committed to submit a type II variation within 2 months after finalisation of the DCP in order to justify the intravesical administration of epirubicin (in the treatment of: Papillary transitional cell carcinoma of the bladder, carcinoma in situ and intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection) by providing relevant data. On 27 January 2009 the MAH has submitted this type II variation (NL/H/1250/001/II/001). The variation is currently in process.

Regulatory

- The MAH committed not to place the product on the market in France until finalisation of the type II variation indicated above (NL/H/1250/001/II/001).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
STS	Soft tissue sarcoma
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Justification for intravesical administration in treatment of bladder carcinoma	NL/H/1250/ 001/MR/II/0 01	II	27-1-2009	10-6-2009	Approval	Y
Change in shape or dimensions of the container or closure	NL/H/1250/ 001/MR/IB/ 002	IB	7-5-2009	6-6-2009	Approval	N
Submission of a new or updated Ph. Eur. Certificate for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance; from a manufacturer currently approved	NL/H/1250/ 001/MR/IA/ 003	IA	27-5-2009	10-6-2009	Approval	N
Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance; tightening of specification limits	NL/H/1250/ 001/MR/IA/ 004	IA	27-5-2009	10-6-2009	Approval	N

ANNEX I – Justification for intravesical administration (NL/H/1250/001/MR/II/001)

For the purpose of this variation the MAH brings up an overview of intravesical administration of epirubicin in the indication bladder cancer, including an overview of comparative efficacy studies of intravesical epirubicin prophylaxis after transurethral resection in patients with superficial bladder cancer.

- Papillary transitional cell carcinoma of the bladder

Although the treatment of superficial bladder cancer is mainly based upon the transurethral resection, additional treatment is needed to reduce the rate of recurrence. Additional intravesical treatment is performed mainly by applying bacillus Calmette-Guerin, although also mitomycin C as well as epirubicin encompass reasonable alternatives, especially when the use of BCG is not feasible (Van der Meijden et al. J Urol, 2001, 166:476-481, Bassi et al. Urol Int, 2002, 68:216-219).
For stage TaT1 primary and recurrent superficial bladder tumours, no clear difference in efficacy was seen between the treatment with epirubicin or mitomycin C (Da Silva et al., 1992).

- In Carcinoma in Situ of the bladder

The primary approach of CIS is mainly TURT. When additional treatment is indicated, in order to prevent local recurrence of residual malignant cells, besides BCG, several chemotherapeutic are recognized as suitable. Intravesical application of epirubicin is an acknowleged treatment option (De Reijke et al. J Urol, 2005, 173: 405–409).

- Prophylaxis for superficial bladder carcinoma

The MAH has submitted an overview of comparative efficacy studies of intravesical epirubicin prophylaxis after transurethral resection in patients with superficial bladder cancer. The effect of epirubicin compared to no prophylaxis, bacillus Calmett-Guerin (BCG), doxorubicin or mitomycin C were studied (see also Table 1).
In the five studies comparing the efficacy of prophylaxis intravesical epirubicin treatment versus no prophylaxis, epirubicin proved to improve the recurrence rate and recurrence free survival (Ali-El Dein et al.Br J Urol. 1997, 79: 731-735, Melekos et al. J Urol. 1992, 147: 371-375; Okamarua et al. Cancer Chemother Pharmacol. 1994, 35 S31-35; Oosterlinck et al. J Urol., 1993, 149: 749-752 and Sengor et al. Int Urol Nephrol.,1996, 26: 201-206).
In the three studies which compared the effect of intravesical BCG versus epirubicin, the clinical efficacy varied. The recurrence rates were consistently significantly lower with BCG than with epirubicin (Melekos et al. Cancer., 1993, 72: 1749-1755, Melekos et al. Oncology, 1996, 53: 281-288 and Melekos et al., Int Urol Nephrol, 1996; 28: 499-509). Whereas in one study the mean recurrence free interval was significantly longer after treatment with BCG in an other study the recurrence free interval seems to be shorter with BCG compared to epirubicin (not significant) (Melekos et al. Cancer., 1993, 72: 1749-1755, Melekos et al. Oncology, 1996, 53: 281-288). Nevertheless, BCG seems to be more effective than epirubicin. Epirubicin remains however an alternative treatment option in cases when BCG is not suitable.
In two studies comparing the efficacy of intravesical prophylaxis with epirubicin with intravesical prophylaxis with doxorubicin, the recurrence rates and mean recurrence free intervals were similar (Ali-El-Dein et al. J Urol., 1997, 158: 68-73 and Schuin et al. Cancer Chemother Pharmacol., 1994, 35: S52-56).

Product information
On the last day of the variation procedure an ‘other concern’ was risen regarding the exact wording of the indication. The MAH committed to add a statement at the end of section 4.1 of the SPC indicating that a positive benefit-risk ratio could only be established in patients in whom live attenuated BCG is contra-indicated or inappropriate. This is not a change to the original indication, but rather a slight modification in order to formulate it more explicitly. The statement will be incorporated upon the first available possibility (e.g. PSUR or variation, whichever comes first).

Conclusion
Although BCG is considered to be the initial intravesical agent of choice in the treatment of superficial bladder cancer, chemotherapeutic alternatives, including epirubicin, are well established intravesical treatment options for carcinoma in situ, pallilary transitional cancer of the bladder and for profylaxis for

recurrence of bladder carcinoma after initial tretament. Also epirubicin can represent an alternative treatment modality for patients that are not suitable to receive live attenuated BCG. In conclusion, the member states consider the indications for epirubicin, for the intravesical treatment of bladder malignancies, approvable.