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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.

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