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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Doxorubicine hydrochloride 2 mg/ml PCH, concentrate for solution for infusion Pharmachemie B.V., the Netherlands

doxorubicin 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/1403/001/DC
Registration number in the Netherlands: RVG 102758

5 August 2010

Pharmacotherapeutic group:	cytotoxic antibiotics and related substances; anthracyclines and related substances.
ATC code:	L01DB01
Route of administration:	intravenous
Therapeutic indication:	acute leukaemias, malignant lymphomas and numerous solid tumours, either alone or in combination therapy regimens with other cytostatic drugs (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	7 July 2010
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, DK, EE, EL, ES, IE, IT, LT, LU, LV, PL, PT, RO, SI, SK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 Doxorubicine hydrochloride 2 mg/ml PCH, concentrate for solution for infusion from Pharmachemie B.V. The date of authorisation was on 7 July 2010 in the Netherlands.

The product is indicated for:
- Breast cancer
- Neoadjuvant and adjuvant therapy of osteosarcoma
- Advanced soft-tissue sarcoma in adults
- Small-cell lung cancer (SCLC)
- Hodgkin's lymphoma
- Highly malignant non-Hodgkin's lymphoma
- Induction and consolidation therapy in acute lymphatic leukaemia
- Acute myeloblastic leukaemia
- Advanced multiple myeloma
- Advanced or recurrent endometrial carcinoma
- Advanced or relapsed papillary/follicular thyroid cancer
- Anaplastic thyroid cancer
- Systemic treatment of local advanced or metastasized bladder carcinoma
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection
- Recurrent ovarian carcinoma
- Wilms' tumour (in stage II in highly malignant variants, all advanced stages [III – IV])
- Advanced neuroblastoma.

Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs.

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

Doxorubicin belongs to the group of anthracyclines and is a cytostatic antibiotic that has been isolated from cultures of *Streptomyces peucetius var. caesius.* It is now prepared semi-synthetically from daunorubicin. Doxorubicin is a strong tissue irritant.
The biological activity of doxorubicin is attributed to its DNA-binding property, which results in inhibition of the enzymatic system, vital for the DNA-replication and the DNA-transcription. The blocking of the cellular cycle seems to be maximal during S phase and mitosis, but inhibition has also been observed during other cell cycle phases.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Adriblastina Soluzione injettabile 50 mg/25 ml, 10 mg/5 ml and 200 mg/100 ml which have been registered in Italy by Pfizer since 19 May 1993 (50 mg/25 ml and 10 mg/5 ml) and 11 October 1999 (200 mg/100 ml). In addition, reference is made to Adriblastina authorisations in the individual member states (reference product). In the Netherlands, Adriblastina R.T.U. solution for injection 2 mg/ml (NL License RVG 13357) was registered on 20 October 1989, but withdrawn for commercial reasons in 2006. The product registered in Italy is used as an EU reference product for the Netherlands, Ireland, Lithuania, Latvia and Poland, where no innovator product is currently authorised.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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 Doxorubicine hydrochloride 2 mg/ml PCH is a product for parenteral use in 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 new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

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
The active substance is doxorubicin hydrochloride, an established active substance not described in the European Pharmacopoeia (Ph.Eur.*). It is an orange-red, crystalline hygroscopic powder, which is soluble in water and slightly soluble in methanol.

The CEP procedure is used for both suppliers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for related substances and residual solvents. The specification is acceptable in view of the CEPs and the various ICH guidelines. Batch analytical data have been provided for the drug substance from both manufacturers, demonstrating compliance with the specification.

Stability of drug substance
Stability data have been provided during storage at 25°C/60%RH and at 40°C/75%RH. The drug substance was packaged in the commercial packaging. The solid drug substance is stable with respect to degradation and light. Based on the data provided, the claimed re-test period of 1 year as applied by the drug product manufacturer is justified; the substance should be stored below 25°C.

** 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
Doxorubicine hydrochloride 2 mg/ml PCH is a clear, red solution with pH 2.7-3.3.

The concentrate for solution for infusion is packed in vials with a nominal volume of 5 ml (10 mg), 10 ml (20 mg), 25 ml (50 mg) or 100 ml (200 mg) colourless glass type I (Ph.Eur.), with a chlorobutyl rubber stopper with an inert fluoropolymer (PTFE) coating on the inner side and with an aluminium seal covered with a coloured polypropylene disc.

The excipients are: sodium chloride, hydrochloric acid (E507), sodium hydroxide (E524), water for injections.

Pharmaceutical development
The development of the product is satisfactorily performed and explained. The excipients are all standard compendial substances that are commonly used in the pharmaceutical industry. The packaging materials are usual and suitable for the product at issue.
The product is a formulation made as a generic version of other doxorubicin containing ready-to-use solutions for injection, which is equivalent to the innovator product Adriamycin PFS. The formulation as a solution in water for injections without preservatives is common and needs no additional justification. No clinical trials or bioequivalence studies were performed. These are not considered necessary, in view of the dosage form (parenteral solution) and the fact that the product has the same composition as the innovator. A 5% overage of the active substance is used for stability reasons. The stability studies of the finished product show a decrease in the content of doxorubicin hydrochloride of more than 5% during 36 months at 2-8°C. The overage is therefore sufficiently justified.
The pharmaceutical development has been sufficiently described.

Manufacturing process
The manufacturing process is non-standard: a solution of the ingredients is made and filled into vials. The active substance is unstable when exposed to heat; therefore sterilisation takes place by sterile filtration. The filtration process sufficiently guarantees the sterility of the finished product. The applied holding time of 168 hours is based on adequate validation data. The sterilizing filtration (2 filters in series) has been adequately validated. From the analytical results of the samples taken during the filling process concluded is that homogeneity of the product meets all requirements during the filling process.

Control of excipients
All specifications are in accordance with the current Ph.Eur. monograph. These specifications are acceptable.

Container Closure System
The glass vials and rubber material of the stopper comply with the Ph. Eur.

Quality control of drug product
The product specification includes all tests as required by the Ph. Eur. monograph on parenteralia. In the first assessment round the MAH was asked to tighten the release and shelf life specifications for impurities. Based on the qualified release and shelf-life specifications, the MAH agreed to apply the proposed release and shelf life specifications for the product.
Batch results for one 5 ml, two 25 ml and two 100 ml vial batches are available at production scale size. Another 5 ml vial batch of production-scale size has been completely analysed as a validation batch. All results meet the set release requirements.

Microbiological attributes
The solution does not contain any preservatives. The integrity of the container closure system to prevent microbial contamination was tested using a dye test. The specification contains an adequate limit for sterility.

Stability of drug product
The product has been stored at 2-8°C and 25°C/60% RH. At 25°C/60%RH significant degradation takes place. Long-term stability data (stored at 2-8°C) are available for 10 batches (up to 24 months). The results of the accelerated studies showed significant degradation. Based on available stability data and the maximum qualified levels for the impurities, a shelf life of 18 months was granted if stored in 5-10-25-

50-100 ml vials at 2-8°C, protected from light. Additional storage condition: *Store in a refrigerator (2-8°C). Do not freeze.*

In-use stability
The in-use stability of the product has been investigated for dilutions with 0.9% sodium chloride and 5% glucose. It is concluded that the diluted product is chemically and physically stable at the final concentration of 0.5 mg/ml doxorubicin per ml at least for 7 days in a refrigerator at 2-8°C or under ambient circumstances (room temperature 15-25 °C and ambient light). However, the product diluted to 0.05% should be used immediately after its preparation. The MAH committed to continue the dilution studies with 0.9% sodium chloride for injection and 5% glucose for injection at the end of its shelf life.

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

This product is a generic formulation of Adriblastina solution for injection, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 doxorubicin 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

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

Doxorubicine hydrochloride 2 mg/ml PCH, concentrate for solution for 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 Doxorubicine hydrochloride 2 mg/ml PCH 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.

Indications
Doxorubicin is a chemotherapeutic agent for a variety of tumour types, either in combination with other cytostatics or as a single agent. In the SPC as proposed, all therapeutic indications (section 4.1), except two (advanced gastric cancer and Wilms’ tumour), are in line with the currently approved indications for Doxorubicin hydrochloride, as represented in the most recent SPC of the completed MRP SE/H/296/001.

In view of the current application, the therapeutic indications for doxorubicin as proposed by the MAH are evaluated in relation to current treatment options. Two additional therapeutic indications, advanced gastric cancer and Wilms’ tumour, were included in the SPC (section 4.1) in comparison to the most recently updated SPC of Doxorubicin after completion of the MRP SE/H/296/001.

The therapeutic indication for advanced gastric cancer is not considered approvable since chemotherapy involving doxorubicin is currently not an acknowledged first or next line treatment regimen for advanced

gastric cancer. Previously it has been shown that treatment with ECF is superior in terms of response rate and median survival when compared to treatment with FAMTX (methotrexate, 5-FU and doxorubicin) in advanced gastric cancer (Webb A *et al*., J Clin. Oncol. 1997). Nowadays, ECF (epirubicin, cisplatin and 5-FU) and DCF (docetaxel, cisplatin and 5-FU) are considered acknowledged treatment regimens for advanced gastric cancer. The exclusion of gastric cancer as therapeutic indication is in line with the most recent SPC of MRP SE/H/296/001 Doxorubicin HCl 2 mg/ml.

For Wilms' tumour, doxorubicin is currently part of a postoperative chemotherapeutic treatment regimen in stage IV cancer when intensification of chemotherapy is necessary, according to International Society of Paediatric Oncology (SIOP) procedure. Wilms' tumour as therapeutic indication is therefore considered approvable, in line with a previously completed MRP procedure (NL/H/334/001).

In view of the current standard for medical care of ovarian cancer, inclusion of ovarian cancer as therapeutic indication is not recommended. To date, platinum agents (especially carboplatin) plus paclitaxel, is the current standard of care (Du Bois A *et al*. Ann. Oncol. 2005; NCCN guideline). Randomized trials failed to show a clear cut, long-term survival advantage for the inclusion of anthracyclines, including doxorubicin, in platinum-based combination regimens (Aravantinos G *et al*. Eur J Cancer. 2008; Thigpen T *et al.* Gynecol. Oncol. 1994). Although benefit has been shown for the combination cyclophosphamide, doxorubicin and cisplatin in the MRC-ICON3 trial, at present doxorubicin is not employed in first and next line treatment options for advanced ovarian cancer.

In view of the other indications sought, the clinical overview on the clinical efficacy and safety is considered adequate. These indications reflect the state of the art use of doxorubicin in clinical practice and are in line with the currently operative guideline on the SPC.

In addition one of the member states requested to change the pharmaceutical form from *solution for injection* to *concentrate for solution for infusion*. This is accepted since it is recommended in the SPC not to administer the product directly without dilution, and since the pharmaceutical form *concentrate for solution for infusion* has been approved for the doxorubicin 2 mg/ml product IE/H/125/001, and is also accepted for other doxorubicin 2 mg/ml containing products.

Risk management plan

Doxorubicin was first approved in 1971, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of doxorubicin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation 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 initially submitted SPC has been amended with respect to therapeutic indications, special warnings and precautions for use, interactions and undesirable effects and is brought in line with the approved SPCs of previously completed European procedures and national innovators.

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The test was scoring: 90% of participants should be able to trace the requested information, of whom at least 90% must be able to show they comprehend it.
The first round of testing showed that 100% of the participants were able to trace the information for the questions, above 90% of the time. Each of these participants showed they understood the information by answering the questions correctly for above 90% of the time.

The second round of testing showed that 100% of the participants were able to trace the information for the questions 100% of the time. Each of these participants showed they understood the information by answering the questions correctly 100% of the time.
Based on the results of the test it was not considered necessary to adapt the leaflet text. In general the conclusions are clear, concise and clearly presented and they reflect the results of the test. Positive feedback from participants focused on layout of the leaflet (bold headings, index, bullet points), however 20% of participants commented the print was too small and the terminology used is complex or medical. Also participants commented there is too much information in the leaflet.
The package leaflet is of sufficient quality to ensure that the relevant information including the key safety messages can be easily found and understood by the most of the patients. The MAH has enlarged the font size from 8 to 9 points to improve the readability.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Doxorubicine hydrochloride 2 mg/ml PCH, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Adriblastina solution for injection 2 mg/ml. Adriblastina is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are 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 doxorubicin 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 Doxorubicine hydrochloride 2 mg/ml PCH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 6 September 2009. Doxorubicine hydrochloride 2 mg/ml PCH, concentrate for solution for infusion was authorised in the Netherlands on 7 July 2010.

A European harmonised birth date has been allocated (15 October 1971) and subsequently the first data lock point for doxorubicin is October 2009. The first PSUR will cover the period from September 2009 to October 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 June 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the in-use stability (dilution) studies with 0.9% sodium chloride for injection and 5% glucose for injection, with an additional 100 ml batch at the end of its shelf life. Results will be submitted as soon as available.

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
DCF	Docetaxel, Cisplatin and 5-FU
ECF	Epirubicin, Cisplatin and 5-FU
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
$t_{½}$	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