CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Doxorubicine HCl Actavis 2 mg/ml, concentrate for solution for infusion Actavis Group PTC ehf, Iceland

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/2251/001/DC
Registration number in the Netherlands: RVG 109099

10 May 2012

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:	27 February 2012
Concerned Member States:	Decentralised procedure with BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, IE, IS, IT, LT, LU, LV, MT, PL, PT, RO, SE, SK, UK
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 HCl Actavis 2 mg/ml, concentrate for solution for infusion from Actavis Group PTC ehf. The date of authorisation was on 27 February 2012 in the Netherlands.

The product is indicated for:

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

Doxorubicin is frequently used in combination chemotherapy regimens with other cytostatic agents.

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

Doxorubicin is an anthracycline antibiotic. The mechanism of action is not completely elucidated. It is postulated that doxorubicin exerts its antineoplastic effect via cytotoxic mechanisms of action, especially intercalation into DNA, inhibition of the enzyme topoisomerase II, and formation of reactive oxygen species (ROS). All of these have a deleterious effect on DNA synthesis: Intercalation of the doxorubicin molecule leads to an inhibition of RNA and DNA polymerases by way of disturbances in base recognition and sequence specificity. The inhibition of topoisomerase II produces single and double strand breaks of the DNA helix. Scission of DNA also originates from the chemical reaction with highly reactive oxygen species like the hydroxyl radical $OH^{\bullet}$. Mutagenesis and chromosomal aberrations are the consequences.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Adryamicin 2 mg/ml solution for injection, which was registered in Denmark by Pfizer on 12 October 1988. 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. In addition, reference is made to Adriblastin authorisations in the individual member states (reference product).

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 HCl Actavis 2 mg/ml, concentrate for solution for infusion 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 described in the European Pharmacopoeia (Ph.Eur.*). The active substance is an orange-red, crystalline, hygroscopic powder, 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 accordance with the Ph.Eur monograph, with appropriate additional specifications included in the CEPs. Particle size and physical form are not relevant as the active substance is dissolved in the manufacturing process of the drug product.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for six production-scale batches.

Stability of drug substance
The active substance is stable for 3 years from one supplier, and for 2 years for the second supplier, when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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 HCl Actavis 2 mg/ml is a clear red solution, with pH 3 (2.8-3.2) and osmolarity 286 mOsm/kg. One ml contains 2 mg of doxorubicin hydrochloride.

The concentrate for solution for infusion is packed in colourless glass vial (type I) with bromobutyl rubber stopper (type I) and sealed with an aluminium cap with polypropylene disk. Available volumes are 5 ml, 10 ml, 25 ml, 50 ml, 75 ml and 100 ml.

The excipients are: sodium chloride, hydrochloric acid 0.1N (for pH adjustment), water for injections.

Pharmaceutical development

The concentration of the active substance is the same as in the originator product. At 2 mg/ml, doxorubicin HCl is soluble at a range of temperatures, so that no precipitation problems occur. The functions of the excipients are straightforward: NaCl for tonicity, acid to achieve the required pH, water for injections as solvent, and nitrogen is used to displace the air in the head-space. The formulation is very simple and identical to the reference product. Studies were carried out to demonstrate essential similarity with the reference product. The batch analysis results are comparable. The product is essentially similar to the reference product. Bioequivalence studies are not required. Sterilisation by heat, dry or in solution, is not feasible, as the drug substance decomposes. Therefore filtration is chosen as the sterilisation method. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The process is a straightforward and consists of dissolution, aseptic sterilisation by filtration and filling. The manufacturing process has been adequately described. Four validation batches for filling volumes of 25 ml and 100 ml were produced to qualify the processing, filtration, filling and testing stages. These batches were manufactured from production-sized bulk batches. These bulk solutions were tested to ensure that the process was valid and in control. Tests on appearance, pH, assay doxorubicin hydrochloride and bioburden complied with the set requirements. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, extractable volume, visible and sub-visible particles, identification doxorubicine HCl, pH, related substances, assay doxorubicine, sterility and bacterial endotoxins. The shelf life specification for the main degradation product and the assay shelf-life requirement are justified; these are wider than the release requirement. The specifications are acceptable in view of the BP Monograph for doxorubicin solution for injection, the Ph.Eur. general requirement for parental preparations, the ICH Guidelines. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production have been provided of six (pilot-scale) batches of all volumes and four (production-scale) batches (3x25 ml and 1x100 ml).

Stability of drug product

Stability data on the product has been provided on one (pilot-scale) batch of all volumes, stored for 9 (2x) and 12 (3x) months at 2-8°C and 6 months at 25°C/60% RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging.

The 12 months batches have been stored in an inverted position, representing the ‘worst case’ storage. Photostability studies have also been performed.

The results of the real time stability studies over 18 months comply with the specifications, although slight trends are observed in assay and related substance results. The accelerated stability studies over 6 months show an expected significant decrease of assay and increase of related substances and confirm the well-known heat-sensitivity of doxorubicin. The product is photolabile and is sufficiently protected in the outer carton.

In view of the provided stability results the proposed shelf for the product of 18 months, if stored at 2-8 °C with the additional storage condition, ‘store in the original outer package to protect from light’, is acceptable.

Compatibility/In-use stability

The stability after first opening of the vials was tested during 28 days; stability was demonstrated for 28 days if stored at refrigerated conditions.
The stability and storage conditions for the prepared infusion solutions have also been studied. Dilutions to 1.25 and 0.5 mg doxorubicine/ml in 0.9% NaCl (PE bottle) and 5% dextrose (PP bag) have been tested for seven days at accelerated and normal storage conditions. The acceptable in-use storage conditions are 24 hours in 5% glucose and for 48 hours in 0.9% sodium chloride at 2°C to 8°C and 25°C, protected from light.

Several commitments have been made with regard to the drug product; these can be found on page 8 of this report.

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 HCl Actavis 2 mg/ml, concentrate for solution for infusion is a parenteral aqueous 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 HCl Actavis 2 mg/ml is comparable to 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
Doxorubicin is one of the leading and commonly used antineoplastic cytotoxic drugs for the treatment of many neoplasms including acute leukaemias, malignant lymphomas and numerous solid tumours. It is administered both as a single agent and as part of combination regimens. The indications for use of doxorubucin are:
- Small-cell lung cancer (SCLC)
- Breast cancer
- ~~Advanced~~ Recurrent ovarian carcinoma
- Intravesical prophylaxis to avoid seeding of superficial bladder carcinoma after the transurethral resection (TUR) of bladder cancer in patients having a great risk of recurrences
- Systemic treatment of local advanced or metastasized bladder carcinoma
- Neoadjuvant and adjuvant therapy of osteosarcoma
- Advanced soft-tissue sarcoma in adult age
- Ewing’s sarcoma
- Hodgkin’s lymphoma

- Highly malignant Non-Hodgkin's lymphoma
- Induction and consolidation treatment in acute lymphatic leukaemia
- Acute myeloblastic leukaemia
- Advanced multiple myeloma
- Advanced or recurrent endometrial carcinoma
- Wilms' tumour (in stage II in highly malignant variants, in all advanced stages [III – IV])
- Advanced papillary/follicular thyroid cancer
- Anaplastic thyroid cancer
- Advanced neuroblastoma
- ~~Advanced gastric carcinoma~~

In view of the current application, the therapeutic indications for doxorubicin as initially proposed by the MAH were evaluated in relation to current treatment options.

For *advanced gastric cancer*, ECF (epirubicin, cisplatin and 5-FU) and DCF (docetaxel, cisplatin and 5-FU) are acknowledged treatment regimens nowadays. Previously it has been shown that treatment with ECF is superiour 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). Chemotherapy involving doxorubicin is at present not considered an acknowledged first or next line treatment regimen for advanced gastric cancer. In line with earlier MR and DC procedures, this indication is **not approvable**.

For *Wilm's tumor*, 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. Wilm's tumour as therapeutic indication is therefore considered approvable, in line with previously completed procedures.

For advanced *ovarian cancer*, doxorubicin has been an established treatment in combination with cyclophosphamide in the past (early 1980). 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 current standard for medical care of ovarian cancer, inclusion of ovarian cancer as therapeutic indication is **not recommended**. In line with other DCPs, the approved wording for this indication is ***Recurrent ovarian carcinoma.***

For *locally advanced breast cancer,* neoadjuvant treatment with an anthracycline-containing combination (e.g., 5-fluorouracil and cyclophosphamide with either doxorubicin (CAF, FAC) or epirubicin (FEC)) is a standard treatment regimen. Anthracyclines are a major component of several multidrug regimens for metastatic breast cancer, among the most widely used being doxorubicin with cyclophosphamide and 5-fluorouracil (5-FU), commonly designated FAC or CAF (Falkson G et al. Eur J Cancer 1991).

In *small-cell lung carcinoma*, a treatment regimen that includes doxorubicin (CAV: cyclophosphamide, doxorubicin and vincristine) can be applied as a second line therapy (Cheng S. et al., J Thorac Oncol. 2007). CAV is reasonably well tolerated and modestly active in patients who have progressed after treatment with a platinum-containing regimen (Shepherd FA, Cancer Treat Rep 1987). Some patients still receive CAV as a potentially less toxic first-line approach.
In *cancer of the thyroid*, doxorubicin is among the most frequent chemotherapeutic agents used in multidrug regimen.

For *advanced urothelial bladder cancer*, the combination chemotherapy regimen methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has been the standard first-line regimen. Nonrandomized studies with the combination of MVAC demonstrated evidence of tumor regression in approximately 70

percent of cases, some of whom had complete responses (Sternberg CN, Cancer 1989). Nowadays, Gemcitabine plus cisplatin (GC) is generally the preferred regimen based upon its decreased toxicity compared to MVAC although MVAC is an acceptable alternative in selected patients with advanced urothelial bladder cancer.

In intermediate-risk and high-risk *neuroblastoma*, multiagent chemotherapy involving doxorubicin is recommended, often applied as neoadjuvant therapy (Matthay KK et al. J Clin Oncol. 1998).

For 'standard' remission induction treatment of *Acute myeloid leukaemia* (especially in younger adults) a combination of an anthracycline and cytarabine is recommended.

For the treatment of *aggressive non-Hodgkin lymphoma*, combination chemotherapy containing an anthracycline is considered imperative.

To date the treatment of *advanced Hodgkin Lymphoma* with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) can be considered as the standard therapeutic treatment.

In treatment of *Ewing's sarcoma* doxorubicin is still part of standard chemotherapy treatment in the VIDE treatment schedule. In that light the indication Ewing's sarcoma is acceptable. Moreover Ewing's sarcoma has been accepted by involved CMS countries in another decentralised procedure.

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, followed by two rounds with 10 participants each. Twenty questions were asked. A quite insensitive scoring system was used, but at the end each of the questions showed whether or not the information could be found and used. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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

The SPC is consistent with that of the reference product. 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 HCl Actavis 2 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 October 2011. Doxorubicine HCl Actavis 2 mg/ml, concentrate for solution for infusion was authorised in the Netherlands on 27 February 2012.

The date for the first renewal will be: 31 June 2016.

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

Quality - medicinal product

- The MAH committed to perform stability studies on the drug product as packaged for sale at 24 months.
- The MAH committed to repeat the stability study on in-use diluted solution as directed in SPC section 6.3 using drug product at the end of 24 months shelf life.
- The MAH committed not to market the medicinal product until 24 months stability data is 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
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