CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Bleomedac 15000 IU (Ph.Eur.), powder for solution for injection medac Gesellschaft für klinische Spezialpräparate mbH, Germany

bleomycin (as sulphate)

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/1792/001/DC
Registration number in the Netherlands: RVG 105676

Date of first publication: 8 February 2010
Last revision: 25 June 2015

Pharmacotherapeutic group:	other cytotoxic antibiotics
ATC code:	L01DC01
Route of administration:	intramuscular, intravenous, intrapleural, intraperitoneal, intra-arterial, local/intratumoral
Therapeutic indication:	Squamous cell carcinoma (SCC) of the head and neck, external genitalia and cervix; Hodgkin's lymphoma; Non-Hodgkin's lymphoma of intermediate and high malignancy in adults; Testis carcinoma (seminoma and non-seminoma); intrapleural therapy of malignant pleural effusion.
Prescription status:	prescription only
Date of authorisation in NL:	17 January 2011
Concerned Member States:	Decentralised procedure with BG, CZ, EE, LT, LV, PL, 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 Bleomedac 15000 IU (Ph.Eur.), powder for solution for injection, from medac Gesellschaft für klinische Spezialpräparate mbH. The date of authorisation was on 17 January 2011 in the Netherlands.

The product is indicated for:
- Squamous cell carcinoma (SCC) of the head and neck, external genitalia and cervix.
- Hodgkin's lymphoma.
- Non-Hodgkin's lymphoma of intermediate and high malignancy in adults.
- Testis carcinoma (seminoma and non-seminoma).
- Intrapleural therapy of malignant pleural effusion.

The administration of bleomycin almost always takes place in combination with other cytostatic drugs and/or radiation therapy.
A comprehensive description of the indications and posology is given in the SPC.

Bleomycin belongs to the cytostatic antibiotics: it is a mixture of structurally related, alkaline, water soluble, glycopeptide antibiotics with a cytostatic effect. The effect of bleomycin rests on intercalation with single and double strands of DNA, resulting in single and double strand ruptures, which inhibit cell division, growth and DNA synthesis.
In a lower degree bleomycin also affects the RNA and protein synthesis. The most important factor in the tissue selectivity of bleomycin is the difference in intercellular inactivity. Cells in the G2 and M phase of the cell cycle are the most sensitive. However, in the past decade more and more evidence has been accumulated that refers to RNA as a possible other molecular target. Squamous cells, with their scarce degree of bleomycin hydrolysis, have a high sensitivity to bleomycin. In sensitive tissues, as well as normal neoplastic tissues, chromosome abnormalities like fragmentation, chromatide ruptures and translocations will be produced frequently.

This decentralised procedure concerns a generic application claiming essential similarity with the historic innovator product Bleomycin Lundbeck, powder for solution for injection 5 mg (NL License RVG 07391) which was registered in the Netherlands by Lundbeck B.V. on 3 August 1977. This product was withdrawn by the MAH in 31 December 1981. In addition, reference is made to innovator Bleomycin authorisations in the individual member states (reference product) and to the European reference product in CMSs where no innovator was registered. The Dutch innovator product Bleomycin Lundbeck serves as a historic European 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. No bioequivalence study is deemed necessary, as Bleomedac 15000 IU (Ph.Eur.) fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions" (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 bleomycin sulphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a mixture of glycopeptides produced by *Streptomyces verticillus* or by any other means. The two principal components of the mixture are Bleomycin A_2 and Bleomycin B_2. The active substance is a white or yellowish white powder which is very soluble in water.

The CEP procedure is used for 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
A CEP has 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. monograph and the CEP. The specification is acceptable in view of the manufacturing process and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification was provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 42 months 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
One 10 ml vial contains 15,000 IU (Ph.Eur) = 15 U (USP) of bleomycin (as bleomycin sulphate).

The product is a cake of white or yellowish white powder in sealed vials.

The powder for solution for injection is packed in colourless type I glass vials with butyl rubber stoppers covered with aluminium caps and polypropylene disks.

Before administration, the lyophilisate is reconstituted and if necessary, further diluted. No excipients are present in the final drug product.

Pharmaceutical development
The development of the product is described. The product does not contain any excipient. The excipients used (water and nitrogen) are common in the manufacture of lyophilisates and are not present in the drug product anymore. As an aqueous solution of the drug substance is not stable over a longer period of time,

a freeze-dried product was developed. The choice of the manufacturing process is justified. The packaging is usual and suitable for the product at issue. No overage or overfill is applied.
As the drug product is applied parenterally, no bioequivalence studies were performed. The quantitative composition of the generic product is identical to the reference product. From a chemical pharmaceutical point of view, the product is considered to be essentially similar to the reference product.
In conclusion, the pharmaceutical development of the product was adequately performed.

Manufacturing process
As the drug product cannot be terminally sterilized, a solution of bleomycin sulphate in water is filtrated through a filter, aseptically filled in vials, after which it is lyophilized. The manufacturing process was adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Microbiological attributes
As terminal sterilisation is not possible, the drug solution is sterilised by filtration, aseptically filled and freeze-dried. The method of sterilisation was adequately justified.

Control of excipients
The product does not contain any excipient.

Quality control of drug product
The product specification for the powder includes tests for appearance, identification, potency, pH, sterility, bacterial endotoxins, copper, loss on drying, appearance of solution, turbidity, foreign insoluble matter, content uniformity and composition. The release and shelf-life limits differ with regard to two of the specifications. An identification test has been included, a test for sub-visible particles and testing harmonized with the Ph.Eur. chapter on uniformity of dosage units. The analytical methods were adequately described and validated.
Batch analytical data from the proposed production site were provided on three production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product was provided for three full-scale batches stored at 5°C (42 months) and at 25°C/60% RH (42 months). The conditions used in the stability studies are according to the ICH stability guideline. The photostability of the drug product has been tested, both the drug substance and the drug product were not affected under diffused light for 27 months in terms of appearances and biological activity.The batches were stored in type I colourless glass vials closed with butylic rubber stoppers and aluminium caps with polypropylene disks. The closed vials were placed in carton boxes.
At 25°C/60% RH, significant changes were observed after 30 months. At 5°C, the product remained stable during the whole period tested. The proposed shelf-life of 36 months and storage condition ‘Store in a refrigerator (at 2 to 8°C)’ are justified.

Compatibility/In-use stability
Bleomedac should be dissolved in physiological saline. After reconstitution in the vial, chemical and physical stability has been demonstrated for 24 hours at 2 °C to 8 °C and for 72 hours at 25 °C. After dilution, chemical and physical stability has been demonstrated for 72 hours at 25 °C in glass bottles and polypropylene syringes.

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 bleomycin sulphate are well known. Preclinical data have been superseded by clinical experience, 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 bleomycin sulphate 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

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

Bleomedac 15000 IU (Ph.Eur.), powder for solution for injection is a parenteral formulation and 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 reference medicinal product (NfG CPMP/EWP/QWP 1401/98). In the case of other parenteral routes, e.g. intramuscular or subcutaneous, if the product is of the same type of solution, contains the same concentration of the same active substance and the same or comparable excipients as the reference medicinal product, then bioequivalence testing is not required.
The quantitative composition of Bleomedac 15000 IU (Ph.Eur.) 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.

Risk management plan
Bleomycin was first approved in 1970, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of bleomycin 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 SPC has been brought in line with the SPC for the bleomycin generic authorised through NL/H/1158/01/DC, and revised according to comments from the member states.

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 two rounds with 10 participants each. The questionnaire consisted of 17 questions on safety issues. Three additional questions requesting feedback of the participant on the layout, design and friendliness of the PIL were also included. The most relevant safety issues were addressed. The result scores were very high. In the first round of testing, for each question, 100% of participants were able to find the correct information and 100% of them were able to answer the questions correctly.
In the second round of testing, for each question, 99% of participants were able to find the correct information, and practically all of them were able to answer the questions correctly. As result of the high scores, no modifications were made to the PIL after the first or second round of testing. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bleomedac 15000 IU (Ph.Eur.), powder for solution for injection has a proven chemical-pharmaceutical quality and is a generic form of the historic reference product Bleomycin Lundbeck solution for injection. Bleomycin Lundbeck is a well-known medicinal product with an established favourable efficacy and safety profile.

Both the reference and current product are intended for parenteral use. No bioequivalence study is deemed necessary, as the current product fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”.

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

The Board followed the advice of the assessors.

The SPC, package leaflet and labelling are in the agreed templates and were in agreement with other bleomycin 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 Bleomedac 15000 IU (Ph.Eur.) with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 22 September 2010. Bleomedac 15000 IU (Ph.Eur.), powder for solution for injection was authorised in the Netherlands on 17 January 2011.

A European harmonised birth date has been allocated (18 March 1970) and subsequently the first data lock point for bleomycin is March 2011. The first PSUR will cover the period from September 2010 to March 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 22 September 2015.

There were no post-approval commitments made during the procedure.

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
Changes in the manufacturing process of the finished product.	NL/H/1792/ 001/IB/001	IB	13-9-2011	14-10-2011	Approval	No
Change in the number of units in a pack.	NL/H/1792/ 001/IB/002	IB	17-8-2011	28-9-2011	Approval	No
Change(s) to the detailed description of the pharmacovigilance system (DDPS).	NL/H/1792/ 001/IA/003	IA	3-8-2011	28-9-2011	Approval	No
Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products.	NL/H/1792/ 001/II/004	II	15-5-2014	26-11-2014	Approval	No