Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Bleomycin 15000 IU Powder for solution for injection/infusion

Bleomycin sulphate

PL 45043/0106

Neon Healthcare Limited

LAY SUMMARY

Bleomycin 15000 IU Powder for solution for injection/infusion
Bleomycin sulphate

This is a summary of the Public Assessment Report (PAR) for Bleomycin 15000 IU Powder for solution for injection/infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Bleomycin in this lay summary for ease of reading.

For practical information about using Bleomycin, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Bleomycin and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Bleo-Kyowa 15,000 IU Powder for Solution for Injection.

Bleomycin is used to treat:
- Certain types of cancer (squamous cell carcinoma) in the head and neck, cervix and external genitalia;
- Certain types of lymph node cancer (e.g. Hodgkin's disease and Non-Hodgkin's lymphoma of intermediate and high malignancy);
- Testicular cancer;
- Fluid accumulation in the lungs (as a result of cancer).

Bleomycin can be used alone, or in combination with other cancer medications, and/or in combination with radiotherapy.

How does Bleomycin work?
Bleomycin contains the active ingredient bleomycin sulphate. Bleomycin is one of a group of medicines called cytostatic medicines. These medicines are anti-cancer medicines sometimes referred to as chemotherapy. They attack cancer cells and prevent them from dividing.

How is Bleomycin used?
The pharmaceutical form of this medicine is a powder for solution for injection/infusion.
The patient's doctor will administer bleomycin into a vein or artery, under the skin, into a muscle, directly into the tumour, or into the space surrounding the lungs (intrapleural), either by injection or using an infusion.

<u>The usual dose:</u>
The (total) dose depends on the indication, patient's age, renal function, and combination with other anticancer medicines. The patient's doctor will set the dose of bleomycin, the duration of the treatment, and the number of treatments. These can vary for each patient.

There is a risk of serious hypersensitivity reaction especially in lymphoma patients which may occur directly or sometime after administration. Therefore, the patient's doctor will give

them a test dose and will observe for 4 hours before starting bleomycin therapy for the first time.

Use in children and adolescents
There is insufficient experience with regard to the administration of bleomycin in children and adolescents. Until more information is available, bleomycin should only be administered in children and adolescents in exceptional circumstances and at special facilities.

For further information on how Bleomycin is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Bleomycin have been shown in studies?
Bleomycin is a generic medicine that fulfils criteria meaning that no additional studies are required. Bleomycin has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics.

What are the possible side effects of Bleomycin?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Bleomycin is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

Why was Bleomycin approved?
It was concluded that, Bleomycin has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Bleomycin?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Bleomycin. The RMP details the important risks of Bleomycin, how these risks can be minimised, any uncertainties about Bleomycin (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Bleomycin.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Bleomycin are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Bleomycin

A marketing authorisation for Bleomycin was granted in the United Kingdom (UK) on 30 November 2023.

The full PAR for Bleomycin follows this summary.

This summary was last updated in February 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Bleomycin 15000 IU Powder for solution for injection/infusion (PL 45043/0106) could be approved.

The product is approved for the following indications:

- Squamous cell carcinoma (SCC) of the head and neck, cervix and external genitalia
- Hodgkin's lymphoma
- Non-Hodgkin’s lymphoma of intermediate and high malignancy in adults
- Testicular carcinoma (seminoma and non-seminoma)
- Intrapleural therapy of malignant pleural effusions.

Bleomycin can be used as a monotherapy but is usually combined with other cytostatics and/or radiation therapy.

Bleomycin 15000 IU Powder for solution for injection/infusion contain bleomycin sulphate. Bleomycin is a mixture of basic, water-soluble glycopeptide-antibiotics with cytotoxic activity. Bleomycin acts by interacting with both single and double- stranded DNA (deoxyribonucleic acid) leading to both single and double-strand scission, which leads in turn to inhibition of cell division, inhibition of growth and inhibition of DNA synthesis. Bleomycin can also influence RNA (ribonucleic acid) and protein biosynthesis to a lesser extent.

The main factor in the tissue selectivity of bleomycin is differences in intracellular inactivation. Squamous cells, with their low bleomycin hydrolase content, are highly sensitive to bleomycin. Chromosome aberrations such as fragmentation, chromatid breaks, and translocations occur in sensitive tissues, both healthy and neoplastic.

Bleomycin can be pyrogenic. It causes little or no bone-marrow toxicity and no immunosuppression.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Bleo-Kyowa 15,000 IU Powder for Solution for Injection that has been licensed for a suitable time, in line with the legal requirements.

No bioequivalence study was required and no new clinical studies were provided with this application.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Bleomycin was granted in the United Kingdom (UK) on 30 November 2023.

II QUALITY ASPECTS

II.1 Introduction

Each vial contains 15,000 International Units (I.U.) of bleomycin (as bleomycin sulphate).

This product contains no excipients.

The finished product is packaged in 5 ml clear type-I glass vial with a grey bromo-butyl rubber closure and green colour flip off top on plain aluminium seal and is available in a pack size of 1 vial.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

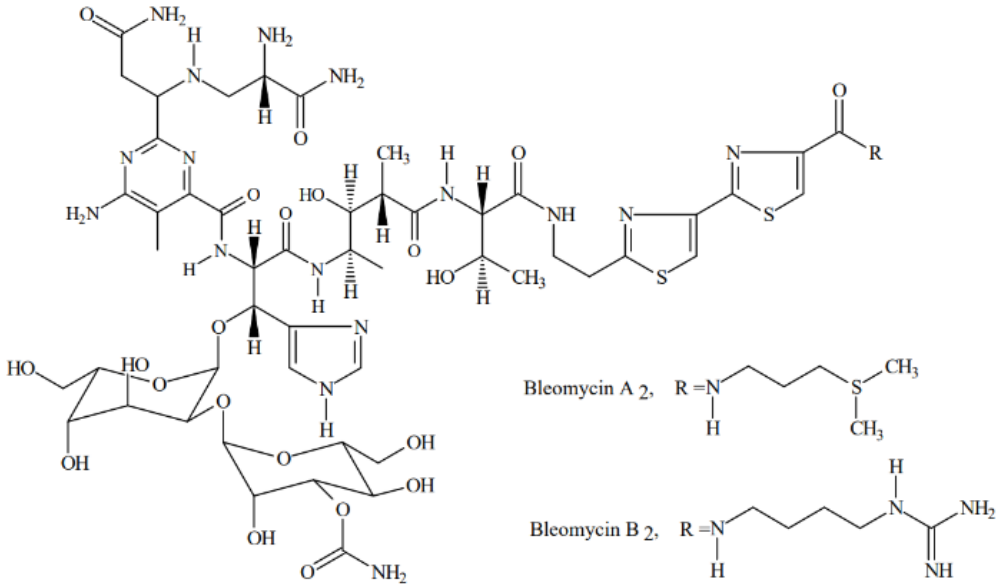
II.2 ACTIVE SUBSTANCE

rINN: Bleomycin sulphate

Chemical Name: Bleomycin sulfate is a mixture of glycopeptides produced by *Streptomyces verticillus* or by other means. The two principal components of the mixture are:
Bleomycin A_2: N1-[3-(dimethylsulfaniumyl)propyl]bleomycinamide
Bleomycin B_2: N1-4-(guanidobutyl) bleomycinamide

Molecular Formula: Bleomycin A_2: $C_{55}H_{84}N_{17}O_{21}S_3$
Bleomycin B_2: $C_{55}H_{84}N_{20}O_{21}S_2$

Chemical Structure:



Molecular Weight: Bleomycin A_2: 1415.6
Bleomycin B_2: 1425.8

Appearance: White or yellowish-white, very hygroscopic powder.

Solubility: Very soluble in water, slightly soluble in anhydrous ethanol, practically insoluble in acetone.

Bleomycin sulphate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months (unopened), with the storage conditions 'Store in a refrigerator (2 °C - 8 °C)', is acceptable.

Once opened: From a microbiological point of view, the reconstituted/diluted product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not normally be longer than 24 hours at 2°C - 8°C.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of bleomycin sulphate are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of bleomycin sulphate is well-known. According to the regulatory requirements, a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV. 2 Pharmacokinetics
No new pharmacokinetic data were submitted for this application, and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application, and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application, and none were required. The safety profile for this product is considered to be the same as Bleo-Kyowa 15,000 IU Powder for Solution for Injection.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Posaconazole 40 mg/ml oral suspension (PL 45043/0009; Neon Healthcare Limited) for design and layout, and to Bleomycin 15000 IU Powder for solution for injection/infusion (PL 20075/0440) for the text. The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with bleomycin sulphate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product. In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**