COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bleomycine Accord 15000 IE powder for solution for injection/infusion (Bleomycin sulphate)

NL/H/4560/001/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Bleomycine Accord 15000 IE powder for solution for injection/infusion. The procedure was finalised in the United Kingdom (UK/H/6023/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Bleomycin 15000 IU Powder for solution for injection/infusion

(Bleomycin sulphate)

Procedure No: UK/H/6023/001/DC

UK Licence No: PL 20075/0440

Accord Healthcare Limited

LAY SUMMARY

Bleomycin 15000 IU Powder for solution for injection/infusion

(Bleomycin sulphate)

The product may be called 'Bleomycin' or 'Bleomycin Powder for solution for injection/infusion' in this report.

This is a summary of the Public Assessment Report (PAR) for Bleomycin Powder for solution for injection/infusion (PL 20075/0440; UK/H/6023/001/DC). It explains how the application for Bleomycin Powder for solution for injection/infusion was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Bleomycin Powder for solution for injection/infusion.

For practical information about using Bleomycin Powder for solution for injection/infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Bleomycin and what is it used for?

Bleomycin Powder for solution for injection/infusion is a 'generic' medicine. This means that Bleomycin Powder for solution for injection/infusion is similar to a 'reference medicine' already authorised in the European Union (EU) called Bleomycine, poeder voor injectievloeistof 15U (15,000 international units [IU], powder for solution for injection; Lundbeck B.V., the Netherlands).

Bleomycin is used to treat:

- certain types of cancer (squamous cell carcinomas) 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 Powder for solution for injection/infusion contains bleomycin (as bleomycin sulphate), as the active substance. 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?

Bleomycin is available as a powder for concentrate for solution for infusion. Bleomycin is administered by a doctor into a vein or artery, under the skin, into a muscle, directly into the tumour, or into the space surrounding the lungs (intrepleural), either by injection or using an infusion.

The patient's doctor will determine the dose of bleomycin, the duration of the treatment, and the number of treatments. These can vary for each patient.

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.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Bleomycin can only be obtained on prescription.

What benefits of Bleomycin have been shown in studies?
No additional clinical studies were needed as Bleomycin is a generic medicine that after reconstitution is an aqueous solution that is given by injection/infusion and contains the same active substance as the reference medicine, Bleo-Kyowa (PL 16508/0046; Kyowa Kirin Limited, formerly known as ProStrakan Limited, UK), which is considered comparable to the reference medicine Bleomycine, poeder voor injectievloeistof 15U (Lundbeck B.V., the Netherlands). Comparison was also made to an EU drug product, Bleomycine® Bellon 15 mg (Bleomycin sulphate for solution for infusion), manufactured by Sanofi-Aventis, which is not licenced in the UK.

What are the possible side effects of Bleomycin?
Like all medicines, Bleomycin used can cause side effects, although not everybody gets them.

Since Bleomycin is a generic medicine and is bioequivalent to the reference medicine, the benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with Bleomycin, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Bleomycin.

Why is Bleomycin approved?
It was concluded that, in accordance with EU requirements, Bleomycin Powder for solution for injection/infusion has been shown to have comparable quality and is considered to be bioequivalent to Bleo-Kyowa (PL 16508/0046; Kyowa Kirin Limited, UK). Therefore, the view was that, as for Bleo-Kyowa (PL 16508/0046; Kyowa Kirin Limited, UK), the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Bleomycin?
A Risk Management Plan has been developed to ensure that Bleomycin used is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Bleomycin, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Bleomycin
Agreement for granting a Marketing Authorisation was given on 10 June 2016 by the UK and the following EU Member States: Austria, Belgium, the Czech Republic, Germany, Denmark, Spain, Finland, France, Italy, the Netherlands, Norway, Poland, Portugal, Romania and Sweden. A Marketing Authorisation was granted in the UK to Accord Healthcare Limited on 08 July 2016.

The full PAR approved for Bleomycin follows this summary.

For more information about treatment with Bleomycin, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2016.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Scientific discussion

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Bleomycin 15000 IU Powder for solution for injection/infusion (PL 20075/0440; UK/H/6023/001/DC) could be approved. The product is a Prescription Only Medicine (POM) and is indicated in the treatment of:

- 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.

The indications for Bleomycin 15000 IU Powder for solution for injection/infusion have been harmonised in line with the conclusion of the bleomycin referral under Article 29 (CHMP/173797/2009) and procedure NL/H/1158/001/DC.

The application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS) and Austria, Belgium, the Czech Republic, Germany, Denmark, Spain, Finland, France, Italy, the Netherlands, Norway, Poland, Portugal, Romania and Sweden as Concerned Member States (CMS).

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Bleomycine, poeder voor injectievloeistof 15U (15,000 international units [IU], powder for solution for injection; Lundbeck B.V., the Netherlands), which was granted on 03 February 1971. This product was withdrawn on 7 July 2000 and no samples of the reference medicinal product could be obtained by the applicant. The applicant has therefore demonstrated equivalence to the marketed reference product Bleo-Kyowa (PL 16508/0046; Kyowa Kirin Limited, formerly known as ProStrakan Limited, UK), which has been approved since 3 July 2006. The application also makes reference to Bleomycine Bellon 15 mg (Sanofi-Aventis), a European Union reference product that is not licenced in the UK.

The active ingredient, bleomycin (as bleomycin sulphate) is a mixture of water-soluble glycopeptide antibiotics with cytotoxic activity (ATC code: L01D C01, other cytotoxic antibiotics). It acts by inducing single strand DNA breaks.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of originator product that has been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application for a parenteral product and the applicant submitted none. According to CPMP guidelines, bioequivalence study are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 208) on 10 June 2016. After a subsequent national phase, a Marketing Authorisation was granted in the UK to Accord Healthcare Limited on 08 July 2016.

II. QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a white to light yellowish freeze dried substance.

Each vial of Bleomycin Powder for solution for injection/infusion contains 15,000 international units (I.U.) of bleomycin (as bleomycin sulphate).

The product also contains sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment).

Appropriate justification for the inclusion of each excipient has been provided.

Bleomycin Powder for solution for injection/infusion is packed in 6 ml Type I tubular clear glass vial, closed with bromobutyl rubber stopper and sealed with a flip-off aluminium seal. The product is available in pack sizes of 1, 10 and 100 vials.

Not all pack sizes may be marketed.

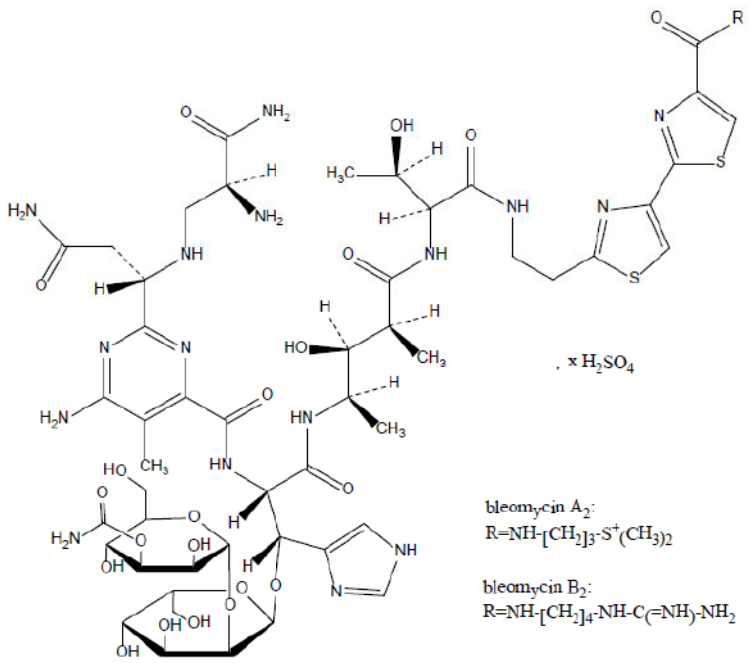
Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with parenteral products.

II.2 DRUG SUBSTANCE

Bleomycin sulphate

INN:	Bleomycin sulphate
Compendial name:	Bleomycin sulfate (Ph. Eur)
Chemical name	Bleomycin A_2: *N*-[3-(dimethylsulfonio)propyl]bleomycinamide
	Bleomycin B_2: *N*-[4-(carbamimidoylamino)butyl]bleomycinamide
Molecular formula:	Bleomycin A_2: $C_{55}H_{84}N_{17}O_{21}S_3$
	Bleomycin B_2: $C_{55}H_{84}N_{20}O_{21}S_2$

Structure:



Mr:	Bleomycin A_2: 1415.55 Bleomycin B_2: 1425.51
Appearance:	White or yellowish-white powder very hygroscopic powder
Solubility:	Very soluble in water, slightly soluble in anhydrous ethanol and practically insoluble in acetone.

Bleomycin sulphate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, bleomycin sulphate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to produce a safe, efficacious, stable powder for solution for injection/infusion that was equivalent to the marketed reference product Bleo-Kyowa (ProStrakan Limited, UK), as the reference product Bleomycine, poeder voor injectievloeistof 15 U (Lundbeck B.V, The Netherlands) was not available. Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for this product and the reference products Bleo-Kyowa (Kyowa Kirin Ltd, ProStrakan Limited, UK) and Bleomycine (Bellon 15 mg; Sanofi-Aventis France), available from the European market. The impurity profiles were satisfactory.

All the excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years for the product in the unopened vial with the special storage conditions "Store in a refrigerator (2°C–8°C)." has been accepted.

The reconstituted/diluted product should be used immediately.

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

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this application for a parenteral product, since Bleomycin 15000 IU Powder for solution for injection/infusion, after reconstitution, is an aqueous parenteral solution containing the same active substance in the same concentration as the currently authorised product, Bleo-Kyowa (ProStrakan Limited, UK).

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Bleomycin 15000 IU Powder for solution for injection/infusion.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of bleomycin are well-known, no new non-clinical data have been submitted and none are required.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion of the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that have been licensed for over 10 years.

It is recommended that a Marketing Authorisation, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of bleomycin is well-known. No new clinical pharmacology data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product and the applicant submitted none. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

All the relevant clinical information provided is literature based. The clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

IV.2 Pharmacokinetics

The pharmacokinetic properties of bleomycin are well known and are adequately described in the applicant's clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.

IV.3 Pharmacodynamics

The clinical pharmacodynamic properties of bleomycin are well-known. No new pharmacodynamic data were submitted and none are required for this type of application.

IV.4 Clinical Efficacy

The clinical efficacy of bleomycin is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety

The safety profile of bleomycin is well known. No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan

The MAH has submitted a Risk Management Plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bleomycin 15000 IU Powder for solution for injection/infusion.

A summary of safety concerns is listed in the table below:

Table: Summary of safety concerns

Important identified risks	Pulmonary toxicity Skin and mucosal lesions Idiosyncratic reactions with fever and chills Myocardial infarction Cerebrovascular insults Thrombotic microangiopathies e.g. haemolytic uraemic syndrome and cerebral arteritis Tumour lysis syndrome Reproductive toxicity
Important potential risks	Carcinogenicity Risk of abortion when exposed during the first trimester of pregnancy
Missing information	Use in paediatric population

Routine pharmacovigilance and risk minimisation measures are proposed. This is acceptable.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted, from a clinical point of view.

V. USER CONSULTATION

A 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 language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Bleomycin 15000 IU Powder for solution for injection/infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

No new clinical data were submitted and none were required for an application of this type. No bioequivalence studies were submitted or required for this application for a parenteral product.

SAFETY

The safety profile of bleomycin is well-known. No new or unexpected safety issues or concerns arose from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT

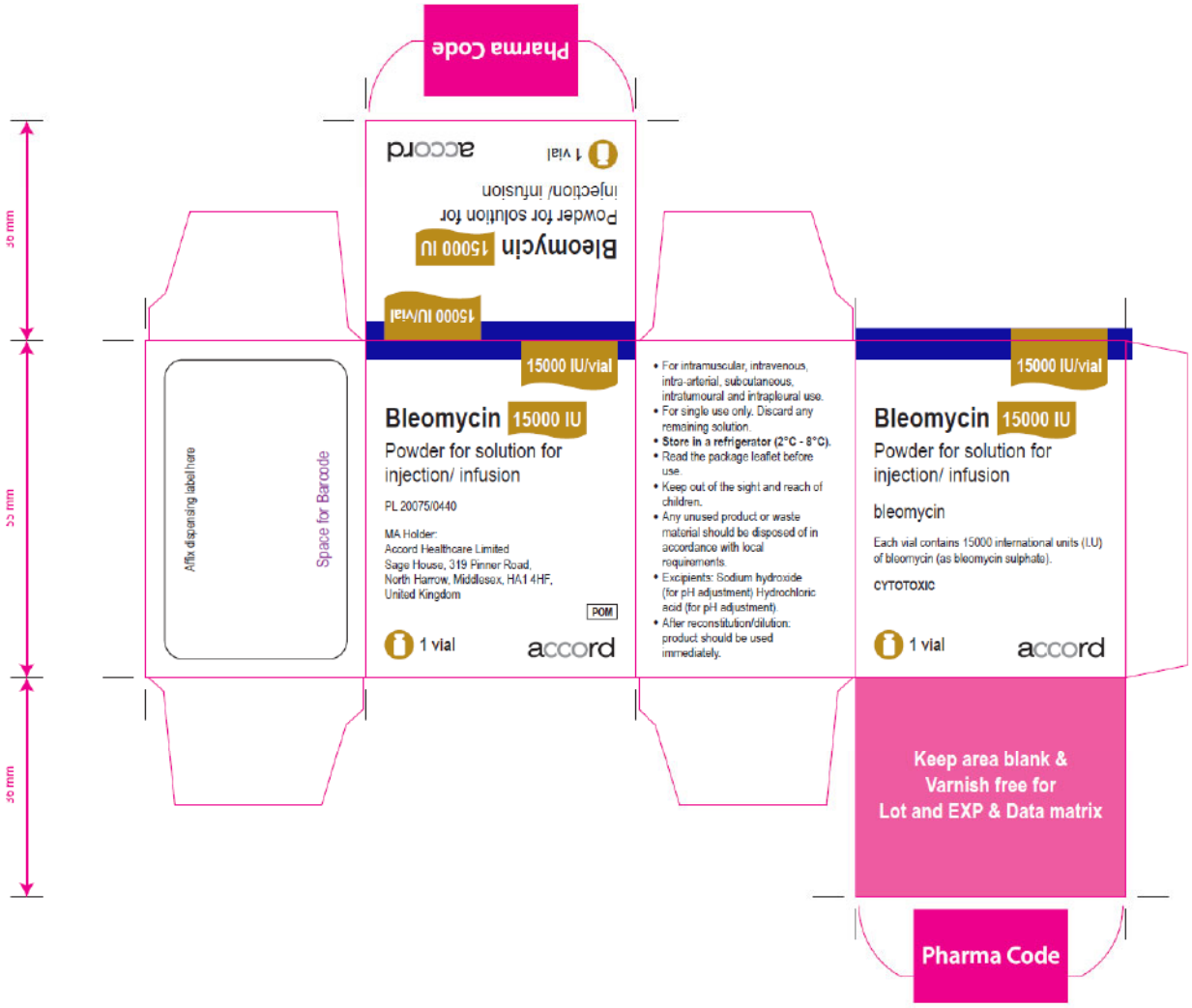
The quality of the product is acceptable, and no new non-clinical safety concerns have been identified. Extensive clinical experience with bleomycin in the proposed indications is considered to have demonstrated the therapeutic value of the compound. The indications for Bleomycin 15000 IU Powder for solution for injection/ infusion have been harmonised in line with the conclusion of the bleomycin referral under Article 29 (CHMP/173797/2009) and Decentralised Procedure NL/H/1158/001/DC. The proposed product is considered bioequivalent to the marketed reference product.

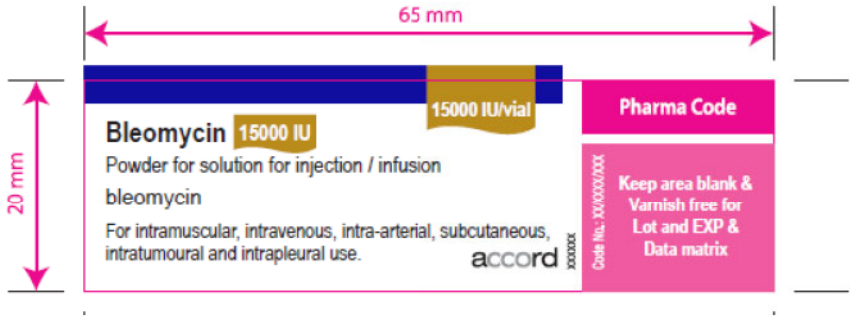
The overall benefit/risk balance is, therefore, considered to be positive.

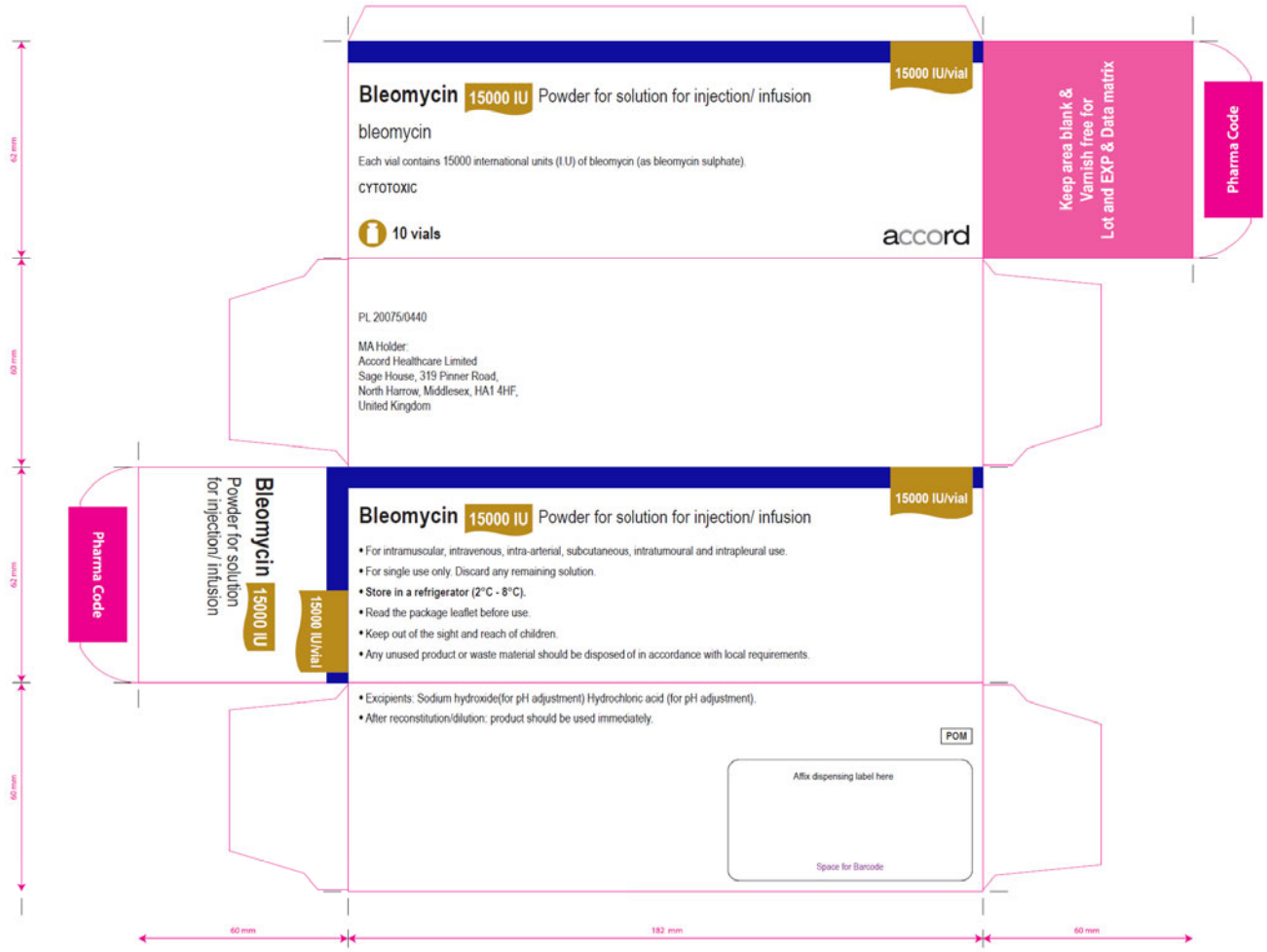
RECOMMENDATION

The grant of a Marketing Authorisation is recommended.

In accordance with Directive 2010/84/EU, the current version of the SmPC and package leaflet is available on the MHRA website. The current labelling is presented below:






Bleomycin 15000 IU Powder for solution for injection/ infusion
bleomycin
Each vial contains 15000 international units (I.U) of bleomycin (as bleomycin sulphate).
CYTOTOXIC
10 vials
accord
15000 IU/vial
Keep area blank & Varnish free for Lot and EXP & Data matrix
Pharma Code
PL 20075/0440
MA Holder:
Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
United Kingdom
Bleomycin 15000 IU Powder for solution for injection/ infusion
• For intramuscular, intravenous, intra-arterial, subcutaneous, intratumoural and intrapleural use.
• For single use only. Discard any remaining solution.
• Store in a refrigerator (2°C - 8°C).
• Read the package leaflet before use.
• Keep out of the sight and reach of children.
• Any unused product or waste material should be disposed of in accordance with local requirements.
• Excipients: Sodium hydroxide(for pH adjustment) Hydrochloric acid (for pH adjustment).
• After reconstitution/dilution: product should be used immediately.
POM
Affix dispensing label here
Space for Barcode
62 mm
60 mm
62 mm
60 mm
60 mm
182 mm
60 mm


120 mm
80 mm
1 X 100 vials
Pharma Code
Bleomycin 15000 IU Powder for solution for injection/ infusion
bleomycin
CYTOTOXIC
Each vial contains 15000 international units (I.U) of bleomycin (as bleomycin sulphate)
• For intramuscular, intravenous, intra-arterial, subcutaneous, intratumoural and intrapleural use.
• For single use only. Discard any remaining solution.
• Store in a refrigerator (2°C - 8°C).
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• After reconstitution/dilution: product should be used immediately.
POM
PL 20075/0440
Accord Healthcare Limited
Sage House, 319 Pinner Road, North Harrow,
Middlesex, HA1 4HF, United Kingdom
accord
Keep area blank &
Varnish free for
Lot and EXP & Data matrix
40 x 25 mm

ANNEX 1-Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)