CBG MEB

Public Assessment Report

Scientific discussion

Mitomycine Accord 2 mg, 10 mg and 20 mg, powder for solution for injection/infusion or intravesical use

(mitomycin)

NL/H/3104/001-003/DC

Date: 24 November 2016

This module reflects the scientific discussion for the approval of Mitomycine Accord 2 mg, 10 mg and 20 mg, powder for solution for injection/infusion or intravesical use. The procedure was finalised on 15 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mitomycine Accord 2 mg, 10 mg and 20 mg, powder for solution for injection/infusion or intravesical use, from Accord Healthcare Ltd.

Mitomycin is indicated for palliative tumour therapy.

Mitomycin is administered intravenously as monochemotherapy or in combined cytostatic chemotherapy in the case of:

- Advanced metastatic gastric carcinoma
- Advanced and/or metastatic breast cancer

Furthermore mitomycin is administered intravenously in combined chemotherapy in the case of:

- Non-small cell bronchial carcinoma
- Advanced pancreatic carcinoma

Mitomycin is also administered intravesically for relapse prevention in superficial urinary bladder carcinoma after transurethral resection.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Mitomycin-C Kyowa 2 mg, 10 mg and 20 mg powder for solution for injection which has been registered in the UK since 26 November 1992 by Kyowa Kirin Limited.

The concerned member states (CMS) involved in this procedure were:
NL/H/3104/001/DC - Austria, Belgium, Czech Republic, Germany, Estonia, Spain, Iceland, Slovakia and the United Kingdom.
NL/H/3104/002/DC - Austria, Belgium, Bulgaria, Czech Republic, Germany, Estonia, Spain, France, Iceland, Italy, Malta, Poland, Portugal, Slovakia and the United Kingdom.
NL/H/3104/003/DC - Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Spain, Finland, France, Poland, Slovenia, Slovakia and the United Kingdom.

A repeat-use procedure (NL/H/3104/001-003/E) was used to register the product in Bulgaria and Malta.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Withdrawal of 40 mg strength
Initially the application included a fourth strength: Mitomycine Accord 40 mg, powder for solution for injection/infusion or intravesical use. However, this strength has been withdrawn from the application before finalisation of the procedure. This was due to observed solubility issues when the product is diluted to a concentration of 1 mg/ml in saline or phosphate buffer. The MAH sufficiently showed that the solubility issues of the 40 mg product have no consequences for the reconstitution of the other strengths, i.e. the vial contents of 2 mg, 10 mg and 20 mg, to a concentration of 1 mg/ml in saline or phosphate buffer.

II. QUALITY ASPECTS

II.1 Introduction

Mitomycine Accord is a blue-violet cake or powder for solution for injection/infusion or intravesical use.

The powder is packed in an amber coloured, type I glass vial with a bromobutyl rubber stopper and an aluminium seal. Each vial contains 2 mg, 10 mg or 20 mg mitomycin. They are intended for

reconstitution with saline or 20% glucose for intravenous use or with saline or phosphate buffer pH 7.4 for intravesical use.

The excipient is mannitol.

II.2 Drug Substance

The active substance is mitomycin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is slightly soluble in water, freely soluble in dimethylacetamide, sparingly soluble in methanol and slightly soluble in acetone.

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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches.

Stability of drug substance
The active substance is stable for three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Justification is given for the choice of the excipient and the container closure system. The excipient mannitol is used as a bulking agent, supporting the freeze-drying process. Nitrogen is used as protective gas.

Therapeutic equivalence was demonstrated to the innovator reference product Mitomycin-C Kyowa. Hence the test and reference were comparable with respect to description, assay and pH, density, viscosity, surface tension and buffer capacity. The related substances level observed in test product is slightly higher compared to the innovator product, due to the fact that the test product is lyophilized powder and the active substance is slightly degraded in the aqueous media during the bulk manufacturing. However the levels of the related substances in the finished product batch release is very well within the specification limit. The test product is considered equivalent to innovator product Mitomycin-C Kyowa.

Manufacturing process
The manufacturing process mainly consists of preparing the bulk solution. Pre-filtration through a bacterial retentive filter and second filtration through a bacterial retentive filter directly followed by filling into bottles. The filled and half stoppered vials are lyophilised. At the end of the freeze drying cycle, the vials are fully stoppered after breaking the vacuum using nitrogen. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three production scale batches per vial strength.

Control of excipients
The excipients comply with pharmacopoeial requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, pH, identity, assay, bacterial endotoxins, related substances, water, uniformity of dosage units by content uniformity, reconstitution time, particulate matter and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The levels of the known impurities could be tightened based on batch analysis and stability data. However, this point is not pursued as the limits for specified impurities are qualified.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data three full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the products have been provided for three full scaled batches per vial strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) for the 2 mg and 20 mg product. At 25°C/60% RH (24 months) and 40°C/75% RH (6 months) for the 10 mg product. The conditions used in the stability studies are according to the ICH stability guideline. The bottles were stored at upright position. The batches were stored in the commercial packaging. At both storage conditions the water content slightly decreased and a very small increase is seen in the total impurities. However all results remain within specifications.
The proposed shelf-life of 2 years with storage condition “This product does not require any special storage conditions" is approvable.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Mitomycine Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Mitomycine Accord is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Mitomycin-C Kyowa which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Mitomycine Accord powder for solution for injection and infusion (administered intravenously) is a parenteral formulation that 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 Mitomycine Accord is entirely the same as the originator.

Mitomycine Accord is also administered intravesically. Therefore, therapeutic equivalence to the innovator should be demonstrated in line with the Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents. The MAH has provided comparative data of the test product against the EU innovator product Mitomycin-C Kyowa in order to show therapeutic equivalence with the innovator product. The MAH compared pH, density, surface tension, viscosity, buffer capacity and osmolality. These parameters are within acceptable values for this kind of product. However, due to differences in excipients, the osmotic value of the product at issue after reconstitution is lower than that of the reference product. The MAH has determined the pH and osmolality of the reconstituted product. This is mentioned in section 6.6 of the SmPC.

Based on the provided data, Mitomycine Accord can 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.

IV.3 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 Mitomycine Accord.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Myelodysplastic Syndrome in case of concomitant administration of other antineoplastic medicinal products • Acute leukaemia and acute myeloid leukaemia in case of concomitant administration of other antineoplastic medicinal products • For the intravesical administration: bladder perforation an/or necrosis • Cardiotoxicity including Cardiac failure • Severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reaction • Administration related reaction • Bone marrow toxicity • Pulmonary toxicities
Important potential risks	• Hepatic toxicity • Severe infections (among which life-threatening and sepsis) • Renal toxicity • Secondary carcinoma • Teratological effect • Gonadal/reproductive toxicity
Missing information	• Use in elderly >65 years of age • Use in children

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Mitomycin-C Kyowa. No new clinical studies were conducted. The MAH demonstrated equivalence based on comparative chemical-pharmaceutical data. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Mitomycine SEP 10 mg and 20 mg, powder for solution for injection/infusion or intravesical use and to the successfully user tested lay-out/design style of the the PL of Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mitomycine Accord 2 mg, 10 mg and 20 mg solution for infusion/injection or intravesical use has a proven chemical-pharmaceutical quality and is a generic form of Mitomycin-C Kyowa 2 mg, 10 mg and 20 mg powder for solution for injection. Mitomycin-C Kyowa is a well-known medicinal product with an established favourable efficacy and safety profile.

Since essential similarity has been sufficiently demonstrated based on quality attributes, no bioequivalence study is deemed necessary.

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 Mitomycine Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 December 2015.

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

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
Deletion of manufacturing site for the active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient. Updated certificate from an already approved manufacturer	NL/H/3104/ IA/001/G	IA	17-2-2016	4-4-2016	Approval	No
Repeat use procedure to register the product in Bulgaria and Malta.	NL/H/3104/ 001-003/E	E	1-6-2016	4-8-2016	Approval	No