CBG MEB

Public Assessment Report

Scientific discussion

Mitomycin Accord 40 mg powder for solution for injection/infusion

(mitomycin)

NL/H/3767/001/DC

Date: 12 March 2019

This module reflects the scientific discussion for the approval of Mitomycin Accord 40 mg powder for solution for injection/infusion. The procedure was finalised on 14 July 2017. 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 Mitomycin Accord 40 mg powder for solution for injection/infusion from Accord Healthcare Limited.

The product 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

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Mitomycin-C Kyowa 40 mg powder for solution for injection which has been registered in the United Kingdom since 26 November 1992 by ProStrakan Ltd. In the Netherlands Mitomycin-C Kyowa 40 mg powder for solution for injection has been registered (NL License RVG 18987) by Takeda Nederland B.V. since 15 February 1996 through a national procedure.

The concerned member states (CMS) involved in this procedure were the Czech Republic, Germany, Estonia, Spain, Italy, Poland, Portugal, Romania, Slovenia, Slovakia and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Mitomycin Accord is a blue-violet cake or powder for solution for injection/infusion

The solution is packed in 100 ml amber coloured type I glass vial with a bromobutyl rubber stopper and a royal blue aluminium seal. Each vial contains 40 mg mitomycin. They are intended for reconstitution with saline or 20% glucose for intravenous use. After reconstitution, 1 ml contains 0.5 mg of mitomycin.

The excipient is mannitol (E421).

II.2 Drug Substance

The active substance is mitomycin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Mitomycin is a blue-violet crystal or crystalline powder. 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. The specification contains additional requirements for solubility, residual solvents, and for microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Batch analytical data demonstrating compliance with this specification have been provided for two pilot scale batches from the drug product manufacturer and three full scale batches from the CEP holder.

Stability of drug substance
The active substance is stable for five 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. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified as well. The type of product does not allow terminal sterilisation. Hence, sterile filtration followed by aseptic processing was chosen. The amber colour of the glass vials is needed to protect the drug product from light. Therapeutic equivalence with the reference product Mitomycin-C Kyowa was established by comparing physicochemical parameters.

Mitomycin products of the same MAH in the strengths of 2 mg, 10 mg, and 20 mg have been approved through procedure NL/H/3104/001-003/DC. These strengths are reconstituted to a concentration of 0.5 mg/ml for intravenous use and to a concentration of 1 mg/ml for intravesical use. The 40 mg strength was part of the previous procedure as well, but it was withdrawn as is can not be reconstituted to a concentration of 1 mg/ml and consequently differs in indications. The lower solubility of the 40 mg strength was adequately explained by the MAH.

As the lower strengths of the product at issue and the 40 mg strengths of other products can be reconstituted to a concentration of 1 mg/ml, it is likely that the product at issue will be reconstituted by health care professionals to a concentration of 1 mg/ml as well. Also as the reconstituted product is blue-violet and the glass vials are amber coloured, incomplete dissolution will not be detected easily and patients may receive a too low dose.

It has been agreed to add warnings to the packaging and product information regarding reconstitution. The implemented additional warnings and instructions are considered sufficient. As reconstitution instructions will be applied by qualified hospital pharmacy personnel, the risk of medication errors is considered negligible.

Manufacturing process
The manufacturing process consists of preparing the bulk solution, pre-filtration through a bacteria retentive filter and second filtration through a bacterial retentive filter directly followed by filling into vials. 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 was adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches in accordance with relevant European guidelines.

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, identification, pH (constituted solution), bacterial

endotoxins, sterility, water, assay, uniformity of dosage units by mass variation, related substances, reconstitution time, particulate matter, clarity of the reconstituted solution, colour of the reconstituted solution, and visible particles of the reconstituted solution. The release and shelf life specification differ with regard to the acceptance criteria for related substances. The proposed drug product specification is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
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 stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No significant changes are seen at both storage conditions. The photostability study shows that product is not sensitive to light in the proposed primary pack.

On the basis of the data submitted, a shelf life was granted of three years. This medicinal product does not require any special storage conditions. The reconstituted product should be used immediately.

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 Mitomycin Accord 40 mg 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 Mitomycin Accord 40 mg 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

Mitomycin Accord 40 mg powder for solution for injection/infusion is a parenteral 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 Mitomycin Accord 40 mg powder for solution for injection/infusion 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.

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 Mitomycin Accord 40 mg.

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 • Cardiotoxicity including cardiac failure • Severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reaction • Administration related reaction • Bone marrow toxicity • Pulmonary toxicities • Microangiopathic-haemolytic anaemia • Renal toxicity
Important potential risks	• Severe hepatic toxicity • Severe infections (among which life-threatening and sepsis) • Secondary carcinoma • Teratological effect • Gonadal/reproductive toxicity • Underdosing due to wrong route of administration/medication error
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 40 mg. 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 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

Mitomycin Accord 40 mg powder for solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Mitomycin-C Kyowa 40 mg powder for solution for injection. Mitomycin-C Kyowa 40 mg is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

In the Board meeting of 14 July 2017, the following was discussed: In daily practice, the proposed product might be administered intravesically. To prevent medication errors, the MAH was requested to add additional instructions regarding reconstitution to the product information. The instructions have subsequently been implemented by the MAH and are considered sufficient.

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 Mitomycin Accord 40 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 July 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse