Public Assessment Report

Decentralised Procedure

MITOMYCIN 40 MG POWDER FOR SOLUTION FOR INJECTION/INFUSION

(mitomycin)

Procedure No: UK/H/5178/001/DC

UK Licence No: PL 04569/1552

Generics (UK) Limited trading as Mylan
This is a summary of the public assessment report (PAR) for Mitomycin 40 mg powder for solution for injection/infusion (PL 04569/1552; UK/H/5178/001/DC). It explains how Mitomycin 40 mg powder for solution for injection/infusion 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 Mitomycin 40 mg powder for solution for injection/infusion.

For practical information about using Mitomycin 40 mg powder for solution for injection/infusion, patients should read the package leaflet or contact their doctor or pharmacist.

**What is Mitomycin 40 mg powder for solution for injection/infusion and what is it used for?**
Mitomycin 40 mg powder for solution for injection/infusion is a ‘generic medicine’. This means that Mitomycin 40 mg powder for solution for injection/infusion is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Mitomycin-C Kyowa 20 mg, poudre pour solution injectable.

Mitomycin is used in cancer therapy for the relief of symptoms (palliative cancer therapy).

**How does Mitomycin 40 mg powder for solution for injection/infusion work?**
This medicine contains the active substance mitomycin. Mitomycin is a medicine for the treatment of cancer. One way in which cancer cells differ from normal cells in the body is that the rate of cell division is increased due to a lack of control of their growth. Mitomycin acts by inhibiting the division of cancer cells by influencing their metabolism in various ways.

**How is Mitomycin 40 mg powder for solution for injection/infusion used?**
This medicine can only be obtained with a prescription.

Mitomycin is intended to be used for injection or infusion into a blood vessel (intravenous use) after being dissolved. Mitomycin should only be administered by healthcare professionals experienced in this kind of therapy. A doctor will prescribe the dose and treatment regimen that is right for the particular patient.

**How has Mitomycin 40 mg powder for solution for injection/infusion been studied?**
The company provided data from the published literature on mitomycin. No additional studies were needed as Mitomycin 40 mg powder for solution for injection/infusion is a generic medicine that is given by infusion and contains the same active substance as the reference medicine, Mitomycin-C Kyowa 20 mg, poudre pour solution injectable.

**What benefits of Mitomycin 40 mg powder for solution for injection/infusion have been shown in studies?**
No studies were needed because Mitomycin 40 mg powder for solution for injection/infusion is a generic medicine that is given as a solution for infusion and contains the same active substance as the reference medicine.

**What are the possible side effects of Mitomycin 40 mg powder for solution for injection/infusion?**
Because Mitomycin 40 mg powder for solution for injection/infusion is a generic medicine, its possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Mitomycin 40 mg powder for solution for injection/infusion, see section 4 of the package leaflet.
For the full list of restrictions, see the package leaflet.

**Why was Mitomycin 40 mg powder for solution for injection/infusion approved?**

It was concluded that, in accordance with EU requirements, Mitomycin 40 mg powder for solution for injection/infusion has been shown to have comparable quality and to be comparable to Mitomycin-C Kyowa 20 mg, poudre pour solution injectable. Therefore, the MHRA decided that, as for Mitomycin-C Kyowa 20 mg, poudre pour solution injectable, the benefits outweigh the identified risks and recommended that Mitomycin 40 mg powder for solution for injection/infusion can be approved for use.

**What measures are being taken to ensure the safe and effective use of Mitomycin 40 mg powder for solution for injection/infusion?**

Safety information has been included in the summary of product characteristics and the package leaflet for Mitomycin 40 mg powder for solution for injection/infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

**Other information about Mitomycin 40 mg powder for solution for injection/infusion**

Austria, Germany, Denmark, Finland, Iceland, Poland, Sweden, Norway and the UK agreed to grant Marketing Authorisations for Mitomycin 40 mg powder for solution for injection/infusion (PL 28176/0121) on 10 April 2014. A Marketing Authorisation was granted in the UK on 16 May 2014.

On 14 November 2014, the licence underwent a change of ownership from Strides Arcolab International Limited (PL 28176/0121) to Generics (UK) Limited (PL 04569/1552).

The full PAR for Mitomycin 40 mg powder for solution for injection/infusion follows this summary. For more information about treatment with Mitomycin 40 mg powder for solution for injection/infusion read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2015.
SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Mitomycin 40 mg powder for solution for injection/infusion (PL 28176/0121; UK/H/5178/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Germany, Denmark, Finland, Iceland, Poland, Sweden and Norway as Concerned Member States (CMS).

This product is a prescription-only medicine (legal classification POM).

This was an application made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Mitomycin-C Kyowa 20mg, poudre pour solution injectable (Nycomed, Belgium), which was initially granted a marketing authorisation in Belgium on 20 June 1961. The corresponding reference product in the UK is Mitomycin-C Kyowa 40 mg powder for solution for injection, which was granted a Marketing Authorisation to Prostrakan Limited (PL 16508/0045) on 09 August 2012. This followed a Change of Ownership from PL 12196/0003, which was granted a Marketing authorisation to Kyowa Hakko Kirin UK Limited on 26 November 1992.

Mitomycin 40 mg powder for solution for injection/infusion is indicated for use in 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

Mitomycin is administered intravenously in combined chemotherapy in the case of:

- non-small cell bronchial carcinoma
- advanced pancreatic carcinoma

This product contains the active substance mitomycin. Mitomycin is a cytostatic medicinal product from the group of alkylating agents.

The mechanism of action is based predominantly on the alkylation of DNA (and to a lesser extent RNA) with the corresponding inhibition of DNA synthesis.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years. In accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), bioequivalence studies are not required for this type of product and none were submitted.

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

The RMS and CMS considered that the application could be approved at the end of procedure on 10 April 2014. After a subsequent national phase, a licence was granted in the UK on 16 May 2014.

On 14 November 2014, the licence underwent a change of ownership from Strides Arcolab International Limited (PL 28176/0121) to Generics (UK) Limited (PL 04569/1552).
II QUALITY ASPECTS

II.1 Introduction
Mitomycin is a powder which is mixed before injection. One vial of powder for solution for injection/infusion contains 40 mg mitomycin. After reconstitution with 80 ml water for injections each ml solution contains 0.5 mg mitomycin.

The finished product is packaged in Type I 100 ml amber moulded glass vials with dark grey bromobutyl lyo stoppers and violet flip-off aluminium seals. The vials are packaged into cartons containing 1, 5 or 10 vials. Not all pack sizes may be marketed.

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

The only excipient in Mitomycin 40 mg powder for solution for injection/infusion is mannitol (E421).

II.2 Drug substance
rINN: Mitomycin
Chemical name(s): [(1aS,8S,8aR,8bS)-6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2',3':3,4]pyrrolo[1,2-a]-indol-8-yl] methyl carbamate (mitomycin C)

Structure:

![Molecular structure of mitomycin C](image)

Molecular formula: C_{15}H_{18}N_{4}O_{5}
Molecular weight: 334.3
Appearance: Blue-violet crystals or crystalline powder.
Solubility: Slightly soluble in water, freely soluble in dimethylacetamide, sparingly soluble in methanol, slightly soluble in acetone.

All aspects of the manufacture and control of the active substance mitomycin from its starting materials 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 formulate a globally acceptable and stable product that could be considered a generic medicinal product of the currently licensed product, Mitomycin-C Kyowa 20mg, poudre pour solution injectable (Nycomed, Belgium).

A satisfactory account of the pharmaceutical development has been provided.
The excipient mannitol complies with its respective European Pharmacopoeia monograph. This excipient is not sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on three batches of finished product. The results are satisfactory.

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

**Stability of the product**
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 2 years for the unopened vial, with the special storage conditions of “Do not refrigerate or freeze”.

Chemical and physical in-use stability has been demonstrated for the reconstituted solution for 24 hours in the recommended diluents stored at 25°C and 2-8°C. After dilution, the solution should be used immediately.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for Mitomycin 40 mg powder for solution for injection/infusion.

**II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The following text is the approved label text. No label mock-ups have been provided for this product. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

1. **NAME OF THE MEDICINAL PRODUCT**

   Mitomycin 40 mg powder for solution for injection/infusion
   mitomycin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   1 vial contains 40 mg of mitomycin

3. **LIST OF EXCIPIENTS**

   Mannitol (E421)

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Powder for solution for injection/infusion
   
   1 X 40 mg
   5 X 40 mg
   10 X 40 mg

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Read the package leaflet before use.
   For intravenous injection or infusion

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

   For single use only
   Cytotoxic Agent

8. **EXPIRY DATE**
9. **SPECIAL STORAGE CONDITIONS**

Do not refrigerate or freeze.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Discard any unused solution immediately after initial use.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 04569/1552

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

15. **INSTRUCTIONS ON USE**

Use as directed by the Physician

16. **INFORMATION IN BRAILLE**

Not applicable.
MINIMUM PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

Mitomycin 40 mg powder for solution for injection/infusion
mitomycin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 40 mg of mitomycin

3. LIST OF EXCIPIENTS

Mannitol (E421)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection/infusion

1 X 40 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous injection or infusion

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only
Cytotoxic Agent

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of mitomycin are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As this product is intended for generic substitution of a product that is already marketed, no increase in environmental exposure to mitomycin is anticipated. Thus the absence of an ERA is accepted.
III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Mitomycin 40 mg powder for solution for injection/infusion.

IV. CLINICAL ASPECTS
IV.1 Introduction
No new clinical data have been submitted and none are required for an application of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No new pharmacokinetic data were submitted with this application and none were required, as per the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). The product is to be administered as an aqueous intravenous solution containing the same active substance as the reference product. There are no excipient interactions which affect the pharmacokinetics of the active substance.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for an application of this type.

IV.5 Clinical Safety
No new data on safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Mitomycin 40 mg powder for solution for injection/infusion.

V. USER CONSULTATION
The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. A bridging report referring to the results of the user consultation study for the package leaflet for the product Mitomycin Strides 40 mg Powder for Solution for Injection (Agila Specialties UK Limited) was provided. 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.
VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with mitomycin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.
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

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