Public Assessment Report

Decentralised Procedure

Mitoxantrone/Strimax 2mg/ml Concentrate for Solution for Infusion

Mitoxantrone hydrochloride

Procedure Nos: UK/H/4634 and 5027/001/DC

UK Licence Nos: PL 28176/0091 & PL 28176/0097

Strides Arcolab International Limited
LAY SUMMARY

On 22 May 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Strides Arcolab International Limited for the medicinal products Mitoxantrone/Strimax 2mg/ml Concentrate for Solution for Infusion (PL 28176/0091 and PL 28176/0097; UK/H/4634 and 5027/001/DC). These are prescription-only medicines (POM). Chemotherapy (treatment with an anti-cancer medicine) with Mitoxantrone/Strimax Concentrate for Solution for Infusion is used in the treatment of breast cancer, adult leukaemia and non-Hodgkin’s lymphoma.

Mitoxantrone/Strimax 2mg/ml Concentrate for Solution for Infusion contains the active ingredient mitoxantrone (as mitoxantrone hydrochloride). It is an anti-cancer medicine belonging to the group of medicines called anthracyclines and related substances.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Mitoxantrone/Strimax 2mg/ml Concentrate for Solution for Infusion outweigh the risks and Marketing Authorisations were granted.
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### Module 1

**Information about the initial procedure**

| **Product Name(s)** | UK/H/4634/001/DC: Mitoxantrone 2mg/ml Concentrate for Solution for Infusion  
UK/H/5027/001/DC: Strimax 2mg/ml Concentrate for Solution for Infusion |
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<tr>
<td><strong>Active Substance(s)</strong></td>
<td>Mitoxantrone hydrochloride</td>
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<tr>
<td><strong>Form</strong></td>
<td>Concentrate for solution for infusion</td>
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<tr>
<td><strong>Strength</strong></td>
<td>2 mg/ml</td>
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| **MA Holder** | Strides Arcolab International Ltd.  
Unit 4, Metro Centre,  
Tolpits Lane, Watford,  
Hertfordshire WD 189SS,  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS) UK/H/4634/001/DC:** | Austria, Germany, Denmark, Finland, Iceland, Norway and Sweden  
**UK/H/5027/001/DC:** | Austria, Belgium, Cyprus, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal and Sweden |
| **Procedure Number(s)** | UK/H/4634/001/DC  
UK/H/5027/001/DC |
| **Timetable** | Day 210 – 18 April 2013 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Mitoxantrone/Strimax 2mg/ml Concentrate for Solution for Infusion (PL 28176/0091 and 0097; UK/H/4634 and 5027/001/DC) could be approved. The products are prescription-only medicines (POM) and are indicated in the treatment of metastatic breast cancer, non-Hodgkin's lymphoma and adult acute non-lymphocytic leukaemia.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Belgium, Cyprus, Germany, Denmark, Greece, Spain, Finland, France, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal and Sweden as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Novantrone 20 mg solución inyectable (Meda Pharma S.A., Spain), which was authorised in Spain on 01 June 1988. The corresponding reference product in the UK is Novantrone Injection 2 mg/mL (Meda Pharmaceuticals Limited, UK), which was first authorised in the UK in June 1984. The reference product is no longer marketed in the UK.

The active ingredient, mitoxantrone (as mitoxantrone hydrochloride), is an anthracenedione antineoplastic agent structurally related to doxorubicin. Mitoxantrone is a DNA-reactive agent, and has a cytocidal effect on proliferating and non-proliferating cultured human cells. In vitro studies suggest that mitoxantrone is not cell-cycle phase specific. Mitoxantrone is indicated in the treatment of metastatic breast cancer, non-Hodgkin's lymphoma and adult acute non-lymphocytic leukaemia. Mitoxantrone has also been used in the palliation of non-resectable primary hepatocellular carcinoma.

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

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for a parenteral product (aqueous solution).

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.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 18 April 2013. After a subsequent national phase, licences were granted in the UK on 22 May 2013.
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | UK/H/4634/001/DC: Mitoxantrone 2mg/ml Concentrate for Solution for Infusion  
UK/H/5027/001/DC: Strimax 2mg/ml Concentrate for Solution for Infusion |
<table>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Mitoxantrone hydrochloride</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Anthracyclines and related substances (ATC code: L01D B07)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Concentrate for solution for infusion; 2 mg/ml</td>
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| Reference number for the Decentralised Procedure | UK/H/4634/001/DC  
UK/H/5027/001/DC |
| Reference Member State (RMS)                     | United Kingdom                                                |
| Concerned Member States (CMS)                    | UK/H/4634/001/DC: Austria, Germany, Denmark, Finland, Iceland, Norway and Sweden  
UK/H/5027/001/DC: Austria, Belgium, Cyprus, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal and Sweden |
| Marketing Authorisation Numbers                  | PL 28176/0091  
PL 28176/0097 |
| Name and address of the authorisation holder     | Strides Arcolab International Ltd.  
Unit 4, Metro Centre,  
Tolpits Lane, Watford,  
Hertfordshire WD 189SS,  
United Kingdom |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Mitoxantrone hydrochloride
Chemical Name: 9, 10 – Anthracenedione, 1, 4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]- dihydrochloride
Molecular formula: C$_{22}$H$_{28}$N$_4$O$_6$.2HCl

Mitoxantrone hydrochloride

Molecular mass: 517.40 g/mol
Appearance: Dark blue powder
Solubility: Sparingly soluble in water (0.1 g in 10 ml) and slightly soluble in methanol.

Mitoxantrone hydrochloride is the subject of a European Pharmacopoeia monograph.

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

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients namely sodium chloride, glacial acetic acid, sodium acetate anhydrous, sodium metabisulfite (E223) and Water for Injections. Appropriate justification for the inclusion of each excipient has been provided.

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

Pharmaceutical Development

The objective of the development programme was to produce a stable formulation of mitoxantrone hydrochloride in a 2 mg/ml concentrate for solution for infusion comparable to the reference product Novantrone 20 mg solución inyectable (Meda Pharma S.A., Spain).

Suitable pharmaceutical development data have been provided for these applications.

Comparative impurity profiles have been provided for this product and the reference product Novantrone 20 mg solución inyectable (Meda Pharma S.A., Spain).

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 and has shown satisfactory results.
Control of Finished Product
The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished product is supplied in 20mm flint type I tubular glass vials filled to 10 ml. The vials are sealed with 20mm grey bromobutyl rubber stoppers and 20mm violet flip off aluminum seals. The product is presented in packs of 1 x10 ml vial.

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

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 18 months has been approved with the storage conditions “Store below 25°C. Do not refrigerate or freeze”.

It is stated that the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

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 these applications for this aqueous solution, parenteral product.

Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PILs) and Labels
The SmPCs, PILs and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

Marketing Authorisation Application (MAA) Forms
The MAA forms are satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of mitoxantrone hydrochloride 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.

An acceptable Environmental Risk Assessment (ERA) has been submitted. The ERA concludes that as this is a generic product, no increase in environmental exposure to mitoxantrone hydrochloride is anticipated following marketing authorisation.

The grant of Marketing Authorisations is recommended.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
No new clinical pharmacology data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for an aqueous parenteral product. 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).

Efficacy
No new efficacy data have been submitted and none are required for applications of this type.

Safety
No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications. As an active ingredient, mitoxantrone hydrochloride has a well-established safety profile and an acceptable level of safety in the proposed indications.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labels
The SmPCs, PILs and labels are acceptable from a clinical perspective. The SmPCs are consistent with that for the innovator product. The PILs are consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with the current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH 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 these applications.

Conclusion
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Mitoxantrone/Strimax 2mg/ml Concentrate for Solution for 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 applications of this type.

EFFICACY
No new clinical data were submitted for these applications. No bioequivalence studies were submitted or required for these applications.

SAFETY
No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the reference product are interchangeable. Extensive clinical experience with mitoxantrone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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