Public Assessment Report
Scientific discussion

Atropin Stragen
(atropine sulphate)

SE/H/1090/02/DC

This module reflects the scientific discussion for the approval of Atropin Stragen. The procedure was finalised on 2016-03-31. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Atropin Stragen, 0.2 mg/ml, solution for injection pre-filled syringe, is a well-established use application made according to Article 10a of Directive 2001/83/EC. The active substance atropine sulphate is the same as in Atropin Stragen, 0.1 mg/ml, solution for injection pre-filled syringe, marketed by Stragen Nordic A/S since 2012. The applicant, Stragen Nordic A/S applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, NO as concerned member states (CMS).

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.
III. NON-CLINICAL ASPECTS

This application was submitted as an abridged application according to Article 10a of Directive 2001/83/EC, as amended, a well-established use application.

Pharmacodynamic, pharmacokinetic and toxicological properties of atropine sulphate are well known. As atropine sulphate is a widely used and well known active substance, this application is based on data from the literature, which is acceptable.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

III.1 Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) has been submitted with this application. The Applicant provided, however, a justification for the absence of ERA assessment. As the atropine is a well-established active substance, which has been in clinical use for many years, no environmental risk assessment is considered necessary.

III.2 Discussion on the non-clinical aspects

Overall the available preclinical information suggests that Atropine Stragen has an acceptable safety pharmacology and toxicity profile for the proposed indications. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and there is no objection to approve Atropine Stragen from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

This is an extension to the 0.1 mg/ml strength which was approved in a well-established use application. No bridging pharmacokinetic studies have been conducted and none are needed for this line extension since the applied strength (0.2 mg/ml solution for injection in prefilled syringe) contains the same excipients as the already approved strength and the product is an aqueous solution for intravenous or intramuscular administration.

IV.3 Pharmacodynamics

Atropine is well-known substance and its mode of action has been thoroughly studied. Atropine is a tertiary amine antimuscarinic alkaloid with both central and peripheral actions that antagonises the action of the parasympathetic neurotransmitter Acetylcholine at muscarinic receptors.

IV.4 Clinical efficacy

The use of atropine in the three applied indications:

- Vagus-induced bradycardia and bradycardiac conditions in which inhibition of vagus-tone is indicated (e.g. sinus bradycardia, atrioventricular block).
- Pre-anaesthetic medication.
- Treatment of an overdose of anticholinesterases as an antidote; in the treatment of poisoning from organophosphorous insecticides or from chemical warfare 'nerve' gases and in the treatment of mushroom poisoning.
are all well established therapies, even if the need in the peri-anaesthetic care has diminished due to changes in anaesthetic techniques. The references in this bibliographic application support the indications. The choice of doses in the proposed SmPC text is also supported in these references.

IV.5 Clinical safety
Atropine is a well-known substance and its safety profile has been established during many decades of frequent use. The drug must be used with care as its potential for causing serious adverse events if used wrongly is considerable.

IV.6 Risk Management Plan
The MAH has submitted a risk management plan (version 0.1 dated 30 April 2015), 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 Atropin Stragen.

Safety specification

An updated RMP has been submitted (Version 0.3)

VI.1.1 Summary table of safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Medication error / Risk of medication error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>Increase in intraocular pressure</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td></td>
</tr>
<tr>
<td>Administration in patients with Myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td>Administration in patients with achalasia of oesophagus, paralytic ileus and obstructive disease of the gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Medication error / Risk of medication error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Long term use / iterative use</td>
<td></td>
</tr>
<tr>
<td>Use in patients with renal or hepatic impairment</td>
<td></td>
</tr>
</tbody>
</table>

Assessor’s comments:

The RMP has been updated in accordance with the RMS’s proposal.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP version 0.3 dated 10 Feb 2016, is approvable.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Atropin Stragen 0.1 mg/ml, SE/H/1090/01/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Atropin Stragen, 0.2 mg/ml, solution for injection pre-filled syringe, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment
N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

The Decentralised procedure for Atropin Stragen, 0.2 mg/ml, solution for injection pre-filled syringe, was positively finalised on 20160331.
Public Assessment Report – Update

<table>
<thead>
<tr>
<th>Procedure number*</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
</tr>
</thead>
</table>

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)