LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Atropin Stragen
(atropine sulphate)

SE/H/1090/01/DC

This module reflects the scientific discussion for the approval of Atropin Stragen. Please note that the marketing authorisation was first approved with the name "Atropine Stragen" and therefore this name is used throughout the document. The procedure was finalised 2012-03-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Stragen Nordic A/S has applied for a marketing authorisation for Atropine Stragen, solution for injection in prefilled syringe, 0.1 mg/ml. The active substance atropine sulphate is a 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 parasympathic neurotransmitter Acetylcholine at muscarinic receptors.
For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Atropine Stragen is presented in the form of a solution for injection in a prefilled syringe containing 0.1 mg/ml of atropine sulfate, which corresponds to 0.083 mg/ml of the atropine base. The excipients are sodium chloride, water for injections and hydrochloric acid for pH adjustment. The solution for injection is filled in a pre-filled syringe.

II.2 Drug Substance

Atropine sulfate has a monograph in the Ph Eur.

Atropine sulfate is a white crystalline powder or colourless crystals, and is very soluble in water. The structure of atropine sulfate has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Atropine Stragen prefilled syringe is formulated using excipients described in the current Ph Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as stability of the drug substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, without any restrictions in storage temperature.

III. NON-CLINICAL ASPECTS

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 studies from the literature.

No environmental risk assessment was presented by the Applicant since in practice this product will be exchange for other atropine product and it will not lead to an increase in the environmental exposure.

IV. CLINICAL ASPECTS

Pharmacokinetics
Atropine has been used during a long period of time by various routes of administration. As atropine was an approved medical product widely used before any pharmacokinetic studies were made, the information on the absorption, distribution, metabolism and elimination of atropine are sparse as compared to new chemical entities approved today. Nevertheless, the applicant has performed a literature survey where the results found have been adequately discussed by the applicant.

Pharmacodynamics
Atropine is a 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 parasympathic neurotransmitter Acetylcholine at muscarinic receptors.

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.

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. The SmPC has been updated during the procedure and the clinical parts are fully acceptable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

If used as recommended in the SmPC, atropine is a very effective drug for treating the applied conditions:

- *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.*

Due to technical innovations and new anaesthetics its use as pre-anaesthetic medication has decreased but it is still very useful in many clinical peri-anaesthetic situations.

The quality of the product, Atropin Stragen 0.1 mg/ml solution for injection in prefilled syringe, is found adequate. There are no objections to approval of Atropin Stragen, from a non-clinical and clinical point of view. The product information is acceptable and the application is recommended for approval.

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
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.

The applicant was requested to amend the layout and the applicant enlarged the font size from 9 pt to 10 pt (correspondingly Times New Roman).

The user test and the package leaflet including layout is acceptable.

The risk/benefit ratio is considered positive and Atropine Stragen is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Atropine Stragen was successfully finalised 2012-03-14.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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