ATROPINE SULFATE 3MG/10ML SOLUTION FOR INJECTION
IN PRE-FILLED SYRINGE
PL 14434/0016

UKPAR

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ATROPINE SULFATE 3MG/10ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE

LAY SUMMARY

The MHRA granted Laboratoire Aguettant a Marketing Authorisation (licence) for the medicinal product Atropine Sulfate 3mg/10ml Solution for injection in pre-filled syringe (PL 14434/0016) on 22 March 2013. This is a prescription-only medicine (POM) used to:

- prevent slow or irregular heart rate during surgery or when a doctor places a tube in your windpipe (tracheal intubation),
- treat slow heart rate in emergency situations,
- control the side effects of neostigmine (a medicine sometimes used after surgery).

It can also be used as an antidote in the following situations:

- Overdose of medicines that block cholinesterase (an enzyme which destroys acetylcholine),
- Poisoning with organophosphate insecticide or gases,
- Poisoning with mushrooms.

The active ingredient atropine sulfate belongs to a group of medicines known as anticholinergics.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Atropine Sulfate 3mg/10ml Solution for injection in pre-filled syringe outweigh the risks, hence a Marketing Authorisation has been granted.
ATROPINE SULFATE 3MG/10ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Laboratoire Aguettant a Marketing Authorisation (licence) for the medicinal product Atropine Sulfate 3mg/10ml Solution for injection in pre-filled syringe (PL 14434/0016) on 22 March 2013. This prescription-only medicine (POM) is indicated for the following:

- As a preoperative medication: to prevent vagal reactions (arrhythmia, bradycardia) associated with tracheal intubation and surgical manipulation.
- In cardiopulmonary resuscitation: to treat sinus bradycardia.
- To treat arrhythmia in acute myocardial infarction: sinus bradycardia, AV conduction block.
- In combination with neostigmine after surgery, to counteract non-depolarising muscle relaxants.
- As a specific antidote following overdosage of anticholinesterases, acute poisoning from organophosphorus (insecticides, chemical warfare nerve gases, carbamates) or muscarinic mushrooms.

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

The drug substance, atropine sulfate is an antimuscarinic agent which competitively antagonises acetylcholine at postganglionic nerve endings, thus affecting receptors in the exocrine glands, smooth muscle, cardiac muscle and the central nervous system.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a well-established use application containing an active substance that has been in clinical use for many years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.
**PHARMACEUTICAL ASSESSMENT**

**DRUG SUBSTANCE**
**Atropine Sulfate**
INN: Atropine sulfate
Chemical name: Bis[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2RS)-3-hydroxy-2-phenylpropanoate] sulphate

Structure:

Molecular formula: C_{34}H_{48}N_{2}O_{10}S, H_{2}O
Molecular weight: 695
Physical form: A white or almost white crystalline powder. Sparingly soluble in water, freely soluble in methanol, practically insoluble in methylene chloride

Atropine sulfate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of atropine sulfate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of atropine sulfate for inclusion in this medicinal product.

Satisfactory specifications have been provided for all materials used in the container-closure of the active substance. Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging. Suitable post approval commitments have been provided to perform follow-up stability studies.

**DRUG PRODUCT**
**Other ingredients**
Other ingredients consist of pharmaceutical excipients, namely sodium chloride, concentrated hydrochloric acid (for pH adjustment) and water for injections. All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

**Pharmaceutical development**
The objective of the pharmaceutical development programme was to produce a safe, efficacious solution for injection containing 3mg atropine sulfate per 10ml, in a pre-filled syringe. The applicant has provided a suitable product development rationale and data.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.
In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on production-scale batches of the finished product. The results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided that comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The 10ml solution is contained in a pre-filled polypropylene syringe, with chlorobutyl rubber plunger stopper, labelled with a polypropylene label in a sterile polypropylene/tyvek blister without needle. The pack sizes are 1, 5, 10, 12, 20, 25, 50 or 100 syringes.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

Not all pack sizes are to be marketed. However, the marketing authorisation holder has committed to submitting mock-ups to the regulatory authorities for approval before marketing any pack size.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, with no specific storage instructions, which is satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are pharmaceutically acceptable.

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 it contains.

**MAA form**
The MAA form is pharmaceutically satisfactory.

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

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

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

No new non-clinical studies were conducted, which is acceptable given that this is a well-established use application containing an active substance that has been in clinical use for many years.

No environmental risk assessment has been submitted with this application. 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.

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

The grant of a marketing authorisation is recommended.

CLINICAL ASSESSMENT

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

No new clinical studies were conducted, which is acceptable given that this is a well-established use application containing an active substance that has been in clinical use for many years.

SAFETY
No new safety concerns have been raised by this application.

EXPERT REPORTS
A clinical expert report has been written by a suitably qualified person and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)
The SmPC is satisfactory and consistent with other similar products.

PATIENT INFORMATION LEAFLET (PIL)
The PIL is satisfactory and consistent with other similar products.

LABELLING
This is satisfactory.

APPLICATION FORM (MAA)
This is satisfactory.

MEDICAL CONCLUSION
The grant of a marketing authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Atropine Sulfate 3mg/10ml Solution for injection in pre-filled syringe 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 an application of this type.

CLINICAL
No new clinical data were submitted and none are required for an application of this type. No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for similar marketed products.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with atropine sulfate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
ATROPINE SULFATE 3MG/10ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE

**STEPS TAKEN FOR ASSESSMENT**

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 30 July 2009</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 05 August 2009</td>
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<td>Following assessment of the application the MHRA requested further information on 13 November 2009, 09 February 2010, 29 July 2011, 30 July 2012 and 23 November 2012</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on 11 May 2010, 31 October 2011, 18 October 2012 and 6 February 2013.</td>
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<td>The application was determined on 22 March 2013.</td>
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ATROPINE SULFATE 3MG/10ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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UKPAR Atropine Sulfate 3mg/10ml Solution for injection in pre-filled syringe

Summary of Product Characteristics and Patient Information Leaflet
The current approved versions of the SmPC and PIL are available on the MHRA website.

Labelling
Atropine sulfate
3 mg/10 ml Solution for injection in pre-filled syringe

Each 10 ml syringe contains 3 mg of atropine sulfate. Each ml of solution contains 0.3 mg of atropine sulfate.

This medicinal product contains 3.5 mg (0.154 mmol) of sodium per ml of injection (a total of 35 mg or 1.54 mmol in 10 ml syringe). This amount must be taken into consideration by patients on a controlled sodium diet.

Sodium chloride, concentrated hydrochloric acid (for pH adjustment), water for Injections. See leaflet for further information.

Solution for injection in pre-filled syringe. 3 mg in 10 ml.

Intravenous use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Do not mix with other medicinal products.

Read the package leaflet before use. To be administered as directed by a medical practitioner.

Marketing Authorisation Holder:
Laboratoire AGUETTANT
1, Rue Alexander Fleming
69007 LYON - FRANCE

Distributed by:
AGUETTANT LTD
The Barn, 41a Aisin Road - Clève
SOMERSET BS49 4HZ - ENGLAND

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