Public Assessment Report

Decentralised Procedure

Oxybutynin hydrochloride 2.5mg/5ml Oral Solution
Oxybutynin hydrochloride 5mg/5ml Oral Solution

(Oxybutynin hydrochloride)

Procedure No: UK/H/5523/001-002/DC

UK Licence No: PL 39307/0022-0023

Syri Limited trading as Thame Laboratories
LAY SUMMARY

Oxybutynin hydrochloride 2.5mg/5ml and 5mg/5ml Oral Solution
(oxybutynin hydrochloride, oral solution, 2.5mg/5ml and 5mg/5ml)

This is a summary of the Public Assessment Report (PAR) for Oxybutynin hydrochloride 2.5mg/5ml Oral Solution (PL 39307/0022; UK/H/5523/001/DC) and Oxybutynin hydrochloride 5mg/5ml Oral Solution (PL 39307/0023; UK/H/5523/002/DC). It explains how Oxybutynin hydrochloride 2.5mg/5ml and 5mg/5ml Oral Solution were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Oxybutynin hydrochloride 2.5mg/5ml and 5mg/5ml Oral Solution.

These products will be collectively referred to as Oxybutynin throughout the remainder of this public assessment report (PAR).

For practical information about using Oxybutynin, patients should read the package leaflet or contact their doctor or pharmacist.

What is Oxybutynin and what is it used for?
Oxybutynin is a ‘generic medicine’. This means that Oxybutynin is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Ditropan 2.5 mg and 5 mg tablets (Sanofi-Aventis, UK).

Oxybutynin can be used in adults and children 5 years or older to treat:
- Loss of control in passing water (urinary incontinence)
- Increased need or urgency to pass water (urine)
- Night time bedwetting, when other treatments have not worked.

How does Oxybutynin work?
Oxybutynin contains an active ingredient called oxybutynin hydrochloride. This belongs to two groups of medicines called ‘anticholinergics’ and ‘antispasmodics’. It works by relaxing the muscles of the bladder and stops sudden muscle contractions (spasms). This helps control the release of water (urine).

How is Oxybutynin used?
The pharmaceutical form of Oxybutynin is an oral solution and the route of administration is via the mouth (oral).

The patient must take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended doses are given below. These may be changed by the patient’s doctor:

Adults
- The usual dose is 5mg two or three times a day
- The patient’s doctor may decide to increase to the maximum dose of 5mg four times a day

Elderly
- The usual dose is 2.5mg twice a day
- The patient’s doctor may decide to increase this to 5mg twice a day

Children (over 5 years)
- The usual dose is 2.5mg twice a day
- The patient’s doctor may decide to increase this to 5mg two or three times a day

If this medicine is to be given to a child to prevent bedwetting, the last dose should be given just before bedtime.

The patient should use the 2.5-5ml double-ended spoon supplied in the pack to measure the required dose. The solution should be swallowed and the spoon washed with clean water after taking every dose.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Oxybutynin can only be obtained with a prescription.

**What benefits of Oxybutynin have been shown in studies?**
Because Oxybutynin is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Ditropan 2.5 mg and 5 mg tablets (Sanofi-Aventis, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Oxybutynin?**
Because Oxybutynin is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with Oxybutynin, see section 4 of the package leaflet available on the MHRA website.

**Why was Oxybutynin approved?**
It was concluded that, in accordance with EU requirements, Oxybutynin has been shown to have comparable quality and to be bioequivalent to Ditropan 2.5 mg and 5 mg tablets (Sanofi-Aventis, UK). Therefore, the MHRA decided that, as for Ditropan 2.5 mg and 5 mg tablets (Sanofi-Aventis, UK), the benefits are greater than their risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Oxybutynin?**
A risk management plan (RMP) has been developed to ensure that Oxybutynin is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Oxybutynin 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/reviewed continuously.

**Other information about Oxybutynin**
Ireland and the UK agreed to grant Marketing Authorisations for Oxybutynin on 27 February 2015. Marketing Authorisations were granted in the UK on 26 March 2015.

The full PAR for Oxybutynin follows this summary.

For more information about treatment with Oxybutynin read the package leaflets, or contact your doctor or pharmacist.

This summary was last updated in May 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Oxybutynin (PL 39307/0022-0023; UK/H/5523/001-002/DC) could be approved. Oxybutynin is a prescription-only medicine (POM) indicated for urinary incontinence, urgency and frequency in the unstable bladder, whether due to neurogenic bladder disorders (detrusor hyperreflexia) in conditions such as multiple sclerosis and spina bifida, or to idiopathic detrusor instability (motor urge incontinence).

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Ditropan 2.5 mg and 5 mg tablets (PL 04425/0289-0290; Sanofi-Aventis, UK) which were originally granted in the UK on 27 February 1987 to Chauvin Pharmaceuticals Limited. These applications subsequently underwent several changes of ownership procedures; the most recent was on 13 May 2009 to the current licence holder Sanofi-Aventis. The Marketing Authorisation Holder (MAH) for the reference products (Sanofi-Aventis) also holds a licence in the UK for a 2.5mg/5ml oral solution called Ditropan Elixir (PL 04425/0286). The reference products cited are acceptable; for the purpose of generic applications, oral immediate release formulations such as tablets and oral suspensions/solutions can be considered interchangeable (NtA, Volume 2A, Chapter 1, 5.3.2.1).

Oxybutynin has both direct antispasmodic action on the smooth muscle of the bladder detrusor muscle as well as an anticholinergic action in blocking the muscarinic effects of acetylcholine on smooth muscle. These properties cause relaxation of the detrusor muscle of the bladder in patients with an unstable bladder. Oxybutynin increases bladder capacity and reduces the incidence of spontaneous contractions of the detrusor muscle.

One bioequivalence study was submitted to support these applications comparing the applicant’s test product Oxybutynin hydrochloride 5mg/5ml Oral Solution with the reference product Ditropan 5 mg tablets (Sanofi-Aventis, UK) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practises (GCP) requirements and the principles enunciated in the Declaration of Helsinki.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on a product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

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 208) on 27 February 2015. After a subsequent national phase, licences were granted in the UK on 26 March 2015.
II QUALITY ASPECTS

II.1 Introduction
Each 5ml of oral solution contains 2.5mg or 5mg oxybutynin hydrochloride. Other ingredients consist of the following pharmaceutical excipients citric acid monohydrate (E330), sodium citrate (E331), liquid sorbitol (non-crystallising) (E420), glycerol (E422), methyl parahydroxybenzoate (E218), raspberry flavour (containing propylene glycol (E1520)) and purified water. Both strengths of the finished product (2.5mg/5ml and 5mg/5ml) are packed into Ph.Eur Type III Amber glass bottles with a tamper evident, child resistant, plastic (polypropylene/polyethylene) cap with EPE liner. The bottles are packed into a cardboard carton together with a dosing device (double-ended white polypropylene plastic spoon with 2.5ml and 5ml measuring ends). The product is available in pack sizes of 100 ml and 150ml bottles. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Oxybutynin hydrochloride
Chemical names: 4-(Diethylamino) but-2-ynyl (RS)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride

Structural formula:

![Structural formula of oxybutynin hydrochloride]

Molecular formula: C_{22}H_{31}NO_{3}*HCl
Molecular mass: 394.0 g/mol
Appearance: A white or almost white crystalline powder.
Solubility: Freely soluble in water and in ethanol (96%). Soluble in acetone and practically insoluble in cyclohexane.

Oxybutynin hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, oxybutynin hydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, oral solution containing 2.5mg or 5mg oxybutynin hydrochloride per 5ml oral solution that was comparable in performance to the originator products Ditropan 2.5 mg and 5 mg tablets (PL 04425/0289-0290; Sanofi-Aventis, UK). A satisfactory account of the pharmaceutical development has been provided.
Comparable *in-vitro* dissolution profiles have been provided for these products and the reference product Ditropan 5 mg tablets.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the raspberry flavour which is controlled to suitable in-house specifications. In addition, confirmation has been provided that the raspberry flavour complies with Directive 88/388/EEC. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacture of the product**
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 at pilot-scale batch size and shown satisfactory results. The MAH has committed to perform process validation on future commercial-scale batch sizes for both strengths.

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

**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. The data from these studies support a shelf-life of 18 months for the unopened bottle with the storage conditions ‘Do not store above 25°C. Discard after 30 days of first opening. Store in the original packaging after first opening.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of oxybutynin hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The MAH’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Oxybutynin is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics
In support of these applications, the MAH submitted the following bioequivalence study:

STUDY
An open label, randomised, single dose, two-treatment, two-sequence, two-period crossover study to compare the pharmacokinetics of the applicant’s test product Oxybutynin hydrochloride 5mg/5ml oral Solution (Syri Limited) versus the reference product, Ditropan 5 mg tablets (PL 04425/0290; Sanofi-Aventis, UK), in healthy adult subjects under fasting conditions.
The subjects were administered a single dose of either the test (5ml of Oxybutynin hydrochloride 5mg/5ml oral Solution) or the reference product (5 mg tablet) with 240 ml of water, after an overnight fast.

Blood samples were collected before and up to and including 24 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Table: Summary of geometric least squares mean, ratios and 90% confidence interval for pharmacokinetic parameters of oxybutynin:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
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<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
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<tr>
<td>C_max (ng/mL)</td>
<td>14.8025</td>
<td>13.7214</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.hr/mL)</td>
<td>28.9016</td>
<td>27.0144</td>
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AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
C_max maximum plasma concentration

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC, and C_max values for oxybutynin lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Ditropan 5 mg tablets (Sanofi-Aventis, UK).

As the 2.5mg/5ml and 5mg/5ml strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 5mg/5ml strength can be extrapolated to the 2.5mg/5ml oral solution strength.

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

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Oxybutynin.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:
No new risks have been identified for these generic products, which are not recognised for the reference products. Overall, the proposed RMP has adequately captured the important identified and potential risks associated with the drug substances.

IV.7 Discussion on the clinical aspects
With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Oxybutynin hydrochloride 5mg/5ml Oral Solution and the reference product Ditropan 5 mg tablets (Sanofi-Aventis, UK), under fasting conditions.

As the 2.5mg/5ml and 5mg/5ml strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 5mg/5ml strength can be extrapolated to the 2.5mg/5ml lower strength.

The grant of marketing authorisations is recommended for these applications.

V 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*.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with oxybutynin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Oxybutynin is presented below:
Each 5ml solution contains 2.5mg oxybutynin hydrochloride. This product also contains liquid sorbitol (non-crystallising) (E420) and methyl parahydroxybenzoate (E218). KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Oxybutynin hydrochloride 2.5mg/5ml Oral Solution

Administration:
For oral use. Use as directed by your doctor. Read the package leaflet before use.

Storage:
Do not store above 25°C. Do not use after the expiry date stated on the packaging after first opening.

Marketing Authorisation Holder:
Synt Limited t/a Thames Laboratories
Unit 4, Bradfield Road, Ruisslip, Middlesex, HA4 0NU, UK.

Size: 110mm x 50mm