Public Assessment Report

National Procedure

Oxybutynin hydrochloride 2.5mg/5ml Oral Solution

Oxybutynin hydrochloride 5mg/5ml Oral Solution

(oxybutynin hydrochloride)

PL 40496/0009-0010

Brill Pharma Limited
Lay Summary

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

(Oxybutynin Hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Oxybutynin hydrochloride 2.5mg/5ml Oral Solution and Oxybutynin hydrochloride 5mg/5ml Oral Solution. It explains how Oxybutynin hydrochloride 2.5mg/5ml Oral Solution and Oxybutynin hydrochloride 5mg/5ml Oral Solution were assessed and their authorisations 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 Oral Solution and Oxybutynin hydrochloride 5mg/5ml Oral Solution.

These products will be referred to as Oxybutynin hydrochloride Oral Solution in this lay summary for ease of reading.

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

What is Oxybutynin Hydrochloride Oral Solution and what is it used for?
These applications are for a generic medicine. This means that these medicines are the same as, and considered interchangeable with, a reference medicines already authorised in the European Union (EU) called Ditropan 2.5 mg tablets and Ditropan 5 mg tablets.

Oxybutynin hydrochloride Oral Solution 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 Hydrochloride Oral Solution work?
Oxybutynin hydrochloride Oral Solution contains a medicine 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 Hydrochloride Oral Solution used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral.

Adults

• The usual dose for Oxybutynin hydrochloride 2.5mg/5ml Oral Solution is 5mg (10ml) two or three times a day. The doctor may decide to increase to the maximum dose of 5mg (10ml) four times a day.
• The usual dose for Oxybutynin hydrochloride 5mg/5ml Oral Solution is 5mg (5ml) two or three times a day. The doctor may decide to increase to the maximum dose of 5mg (5ml) four times a day.
Elderly
- The usual dose for Oxybutynin hydrochloride 2.5mg/5ml Oral Solution is 2.5mg (5ml) twice a day. The doctor may decide to increase this to 5mg twice a day.
- The usual dose for Oxybutynin hydrochloride 5mg/5ml Oral Solution 2.5mg (2.5ml) twice a day. The doctor may decide to increase this to 5mg (5ml) twice a day.

Children (over 5 years)
- The usual dose for Oxybutynin hydrochloride 2.5mg/5ml Oral Solution 2.5mg (5ml) twice a day. The doctor may decide to increase this to 5mg (10ml) two or three times a day.
- The usual dose for Oxybutynin hydrochloride 5mg/5ml Oral Solution 2.5mg (2.5ml) twice a day. The doctor may decide to increase this to 5mg (5ml) two or three times a day.
- If this medicine is being given to a child to prevent bedwetting, give the last dose just before bedtime.

Method of Administration
Use the enclosed 5 ml oral syringe (graduated at every 0.5 ml) together with the enclosed adaptor to attach the syringe to the bottle. This will help to take a dose from the bottle.

For further information on how Oxybutynin hydrochloride Oral Solution is used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Oxybutynin hydrochloride Oral Solution have been shown in studies?
Either
Because Oxybutynin hydrochloride Oral Solution is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. 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 hydrochloride Oral Solution?
Because Oxybutynin hydrochloride Oral Solution is a generic medicine and is bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why was Oxybutynin hydrochloride Oral Solution approved?
It was concluded that, in accordance with EU requirements, Oxybutynin hydrochloride Oral Solution has been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Oxybutynin hydrochloride Oral Solution?
A Risk Management Plan (RMP) has been developed to ensure that Oxybutynin hydrochloride Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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 and reviewed continuously.

**Other information about Oxybutynin hydrochloride Oral Solution**

Marketing Authorisations for Oxybutynin hydrochloride Oral Solution were granted in the UK to the Marketing Authorisation Holder (MAH) LIQMEDS Limited on 10 April 2019. A change of ownership procedure took place on 30 April 2019 to the current Marketing Authorisation Holder Brill Pharma Limited.

The full PAR for Oxybutynin hydrochloride Oral Solution follows this summary.

This summary was last updated in 05-2019.
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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Oxybutynin hydrochloride 2.5mg/5ml Oral Solution and Oxybutynin hydrochloride 5mg/5ml Oral Solution (PL 40496/0009-0010) could be approved.

The product is indicated for the treatment of the following:

- 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).

Paediatric population
Oxybutynin hydrochloride is indicated in children over 5 years of age for:

- Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor overactivity).

- Nocturnal enuresis associated with detrusor overactivity, in conjunction with non-drug therapy, when other treatment has failed.

Oxybutynin hydrochloride is the active substance in these products. 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.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines. The reference medicinal products are Ditropan 2.5 mg tablets and Ditropan 5 mg tablets (PL 04425/0289-0290), which were originally granted product licences to Chauvin Pharmaceuticals Limited (PL 00033/0124-0125) on 31 December 1993. Following several change of ownership procedures, the product licences were granted in the UK to the current MAH; Aventis Pharma Limited trading as Sanofi-Aventis on 26 March 2009 and 15 March 2009, respectively. The reference product holder Sanofi-Aventis also held a license in the UK for a 2.5 mg/5 ml oral solution called Ditropan Elixir (PL 04425/0286) until 04/01/2016 when it was cancelled.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being a generic medicinal products of a reference products that have been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this/these products at all sites responsible for the manufacture, assembly and batch release of this/these products.
A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this/these applications and are satisfactory.

Marketing Authorisations for Oxybutynin hydrochloride 2.5mg/5ml Oral Solution and Oxybutynin hydrochloride 5mg/5ml Oral Solution were granted in the UK to the Marketing Authorisation Holder (MAH) LIQMEDS Limited on 10 April 2019. A change of ownership procedure took place on 30 April 2019 to the current Marketing Authorisation Holder Brill Pharma Limited.
II QUALITY ASPECTS

II.1 Introduction
Each 5 ml oral solution consists of either 2.5mg or 5mg of the active substance oxybutynin hydrochloride.

The oral solution is Oral solution is a clear, colourless solution with characteristic raspberry odour.

In addition to oxybutynin hydrochloride, these products also contain the excipients sodium benzoate (E211), citric acid monohydrate (E330), sodium citrate (E331), sucralose (E955) raspberry flavor and purified water.

Oxybutynin hydrochloride Oral Solution is packaged in 150 mL amber coloured Type III glass bottle with a child resistant 28 PP closure CRC-TE with EPE liner, packed in a carton.

Each carton contains 1 bottle and a 5 ml oral syringe with adaptor (graduated at every 0.5 ml).

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE
rINN: oxybutynin hydrochloride

Chemical Name: 4-(Diethylamino) but-2-ynyl (RS)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride

Molecular Formula: C_{22}H_{31}NO_{3}HCl

Chemical Structure:

Molecular Weight: 394.0

Appearance: White or almost white, crystalline powder

Solubility: Freely soluble in water and in ethanol (96%). Soluble in acetone, 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
II.3 DRUG PRODUCT
Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European monographs, and suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions ‘Discard after 30 days of first opening. Store in the original packaging after first opening. Store in the original container in order to protect from light’, is acceptable.

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
The grant of a marketing authorisations is recommended.

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

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of an already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of oxybutynin hydrochloride is well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this/these study is, thus, satisfactory.

IV.2 Pharmacokinetics

In support of the application, the applicant submitted the following:

STUDY

This study was an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing the test product Oxybutynin hydrochloride 5mg/5ml Oral Solution (Dose: 5mg) versus the reference product Ditropan 5mg tablets in subjects under fasted conditions.

Subjects were administered a single oral dose of either the test or reference product in the fasting state. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

<table>
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<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric Mean Ratio Test/Ref</th>
<th>Confidence Intervals</th>
<th>CV %</th>
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<td>AUC&lt;sub&gt;D&lt;sub&gt;t&lt;/sub&gt;&lt;/sub&gt;</td>
<td>108.77</td>
<td>101.62 - 116.42</td>
<td>22.35</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>103.75</td>
<td>95.62 - 112.58</td>
<td>27.00</td>
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In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Cort**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strength; Oxybutynin hydrochloride 2.5mg/5ml Oral Solution.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.
IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this/these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisations is recommended for this/these applications.

V USER CONSULTATION
A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Oxybutynin hydrochloride 2.5mg/5ml Oral Solution (PL 39307/0022) and Oxybutynin hydrochloride 5mg/5ml Oral Solution (PL 39307/0023). The bridging report submitted by the MAH is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product 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.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below:
Oxybutynin hydrochloride 2.5mg/5ml and 5mg/5ml Oral Solution

Ingredients:
- Oxybutynin hydrochloride 2.5mg/5ml
- Oxybutynin hydrochloride 5mg/5ml

Packaging:
- 150ml bottle

Uses:
- Oral solution

Storage:
- Keep out of the sight and reach of children.
- Store in the original container in order to protect from light.
- The product should be discarded 30 days after first opening the bottle.
Each 5ml of oral solution
contains 5 mg of
Oxybutynin hydrochloride
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of
children.
Store in the original container in
order to protect from light.
The product should be discarded
30 days after first opening the bottle.
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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

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<thead>
<tr>
<th>Application type</th>
<th>Scope</th>
<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Outcome</th>
<th>Assessment report attached Y/N</th>
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Generic, Article 10(1)