IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Oxybutynin hydrochloride 2.5 mg/5 ml oral solution
OXYBUTYNIN HYDROCHLORIDE
PA22697/014/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5523/1-2/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 03/10/2018 under procedure number IE/H/0782/1-2/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/014/001-002
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

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 QUALITY ASPECTS

II.1 Introduction

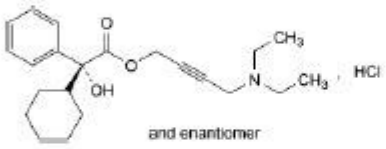
Each 5ml of oral solution contains 2.5mg or 5mg oxybutynin hydrochloride. Other ingredients consist of the following pharmaceutical excipients citric acid monohydrate (E330), sodium citrate (E331), liquid sorbitol (non-crystallising) (E420), glycerol (E422), methyl parahydroxybenzoate (E218), raspberry 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:



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 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 CLINICAL ASPECTS

IV.1 Introduction

IV.1 Introduction

The clinical pharmacology of oxybutynin hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of oxybutynin hydrochloride.

Based on the data provided, Oxybutynin be considered bioequivalent to Ditropan 2.5 mg and 5 mg tablets (Sanofi-Aventis, UK).

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:

Pharmacokinetic Parameters (Units)	Ln- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)	
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	14.8025	13.7214	107.88	98.45	118.21
AUC_{0-t} (ng.hr/mL)	28.9016	27.0144	106.99	100.46	113.93

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:

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Use in patients with myasthenia gravis • Use in patients with glaucoma • Use in patients with gastrointestinal disorders (including ulcerative colitis toxic megacolon, paralytic ileus and intestinal atony) • Use in patients with urinary bladder outflow obstruction • Use in patients with heart disease • Inhibition of sweating • Overdose • Use in patients with fructose intolerance • Effect on ability to drive and use machines
Important potential risks	• Use in elderly and in patients sensitive to the effects of the drug product (particularly children)
Missing information	• Use during pregnancy and lactation • Use in children less than 5 years of age

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.*

V. OVERALL CONCLUSIONS

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.

VI. REVISION DATE

23/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5523/1-2/DC to IE/H/0782/1-2/DC			