Public Assessment Report

UKPAR

Trospium chloride 20mg film-coated tablets

(Trospium chloride)

UK Licence Number: PL 42176/0010

Lucis Pharma Limited.
LAY SUMMARY

Trospium chloride 20mg film-coated tablets
(trospium chloride)

This is a summary of the Public Assessment Report (PAR) for Trospium chloride 20mg film-coated tablets (PL 42176/0010). It explains how Trospium chloride 20mg film-coated tablets 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 Trospium chloride 20mg film-coated tablets.

This product will be referred to as Trospium chloride tablets throughout the remainder of this public assessment report (PAR).

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

What are Trospium chloride tablets and what are they used for?
Trospium chloride tablets are a ‘generic medicine’. This means that Trospium chloride tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, UK).

This medicine is used for the treatment of symptoms associated with involuntary loss of urine (wetting) and/or increased frequency of urination and imperative urge of urination in patients with active bladder (involuntary urge of urination and voiding problems of unknown origin or due to nervous system disorders).

How do Trospium chloride tablets work?
This medicine contains the active ingredient trospium chloride which is used for relaxation of the bladder; it works by preventing the bladder muscles from contracting too frequently and uncontrollably (which occurs with an overactive bladder).

How are Trospium chloride tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

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.

Usual dose:
Unless otherwise prescribed by their doctor, the usual daily dose for adults and children over the age of 12 years is one Trospium chloride tablet taken twice daily (equivalent to 40 mg of trospium chloride daily).

Method of administration
Swallow one tablet whole with a glass of water. Take the tablet before a meal on an empty stomach.

Duration of treatment
The patient’s doctor will determine the duration of treatment. The need for continued treatment should be checked by the patient’s doctor at regular intervals of 3-6 months.

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

For further information on how Trospium chloride tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Trospium chloride tablets have been shown in studies?**
Because Trospium chloride tablets are a generic medicine, studies have been limited to tests to determine that they are bioequivalent to the reference medicine Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, 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 Trospium chloride tablets?**
Because Trospium chloride tablets are a generic medicine and are bioequivalent to the reference medicine Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, UK), their benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

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

**Why were Trospium chloride tablets approved?**
It was concluded that, in accordance with EU requirements, Trospium chloride tablets have been shown to have comparable quality and to be bioequivalent to Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, UK). Therefore, the MHRA decided that, as for Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, UK), the benefits are greater than the risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Trospium chloride tablets?**
A risk management plan (RMP) has been developed to ensure that Trospium chloride tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Trospium chloride tablets 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 Trospium chloride tablets**
A Marketing Authorisation was granted in the UK on 24 May 2018.

The full PAR for Trospium chloride tablets follows this summary.

For more information about treatment with Trospium chloride tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2018.
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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) granted Lucis Pharma Limited, a marketing authorisation for the medicinal product Trospium chloride tablets (PL 42176/0010) on 24 May 2018. The product is a prescription-only medicine (POM) and is indicated for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder (e.g. idiopathic or neurologic detrusor overactivity).

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Regurin 20 mg coated tablets which was first authorised to Madaus AG on 14 September 2000 (PL 04638/0013) and underwent several changes of ownership procedures of which the most recent was to the current marketing authorisation holder (MAH), Meda Pharmaceuticals Ltd (PL 15142/0285), on 05 July 2016.

Trospium chloride is a quaternary derivative of nortropane and therefore belongs to the class of parasympatholytic or anticholinergic drugs, as it competes concentration-dependently with acetylcholine, the body's endogenous transmitter at postsynaptic, parasympathic binding sites.

Trospium chloride binds with high affinity to muscarinic receptors of the so called M1-, M2- and M3-subtypes and demonstrates negligible affinity to nicotinic receptors.

Consequently, the anticholinergic effect of trospium chloride exerts a relaxing action on smooth muscle tissue and organ functions mediated by muscarinic receptors. Both in preclinical as well as in clinical experiments, trospium chloride diminishes the contractile tone of smooth muscle in the gastrointestinal and genito-urinary tract.

Furthermore, it can inhibit the secretion of bronchial mucus, saliva, sweat and the ocular accommodation. No effects on the central nervous system have so far been observed.

One bioequivalence study (conducted under fasting conditions) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with good clinical practice (GCP).

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 being a generic medicinal product of an originator product that has been in clinical use for over 10 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.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Trospium chloride tablets outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 20 mg trospium chloride, as the active ingredient. Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, croscarmellose sodium, Povidone K-25, magnesium stearate.

Coating blend:
Hypromellose 2910, titanium dioxide, polydextrose, talc, maltodextrin, medium chain triglycerides and iron oxide.

The finished product is packaged in polyvinyl chloride (PVC) foiled blisters in pack sizes of 20, 30, 50, 60 and 100 film-coated tablets. 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: Trospium chloride
Definition: \((1R,3r,5S)-3-[(\text{Hydroxydiphenylacetyl})\text{oxy}]\text{spiro}[8-\text{azoniabicyclo}[3.2.1]octane-8,1'-pyrrolidinium}]\) chloride.

Structure:

![Structure of Trospium Chloride]

Molecular formula: \(C_{25}H_{30}ClNO_3\)
Molecular weight: 428.0 g/mol
Description: White or almost white, crystalline powder.
Solubility: Very soluble in water, freely soluble in methanol, practically insoluble in methylene chloride.

Trospium chloride is the subject of a European Pharmacopoeia monograph.

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

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious film-coated tablets containing 20 mg trospium chloride per tablet, that are generic versions of the reference product Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, UK). A satisfactory account of the pharmaceutical development has been provided.
Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the coating blend which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

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

**Manufacture of the product**
As 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 has shown satisfactory results. The process validation protocol to be followed for future production batches has also been provided and is satisfactory.

**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 which comply with the release specification. 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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with no special storage conditions ‘Store in the original package.’

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 this application from a pharmaceutical viewpoint.

**III NON-ClinICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of trospium chloride 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 applicant’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 Trospium chloride tablets are 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
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of trospium chloride 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 trospium chloride.

Based on the data provided, Trospium chloride tablets can be considered bioequivalent to Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, UK).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
An open label, balanced, randomised, two-treatment, two-sequence, four-period, single oral dose, fully replicated, crossover bioequivalence study of the applicant’s test product Trospium chloride 20mg film-coated tablets (Lucis Pharma Limited) versus the reference product Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, UK) in healthy adult subjects under fasting conditions.

Subjects were administered a single dose (1x 20 mg tablet) of the test or reference product after an overnight fast of at least 10 hours.

Blood samples were collected for plasma levels before dosing and up to and including 108 hours after each administration. The washout period between the treatment phases was 16 days. The pharmacokinetic results are presented below:
Table: Summary of pharmacokinetic data for trospium (ratio and 90% confidence intervals of test versus reference product):

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Means</th>
<th>90% Confidence Interval</th>
<th>Acceptance Criteria (%)</th>
<th>Intra-subject CV of Reference Product-R (%)</th>
<th>Power (%)</th>
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<tbody>
<tr>
<td></td>
<td>Test Product-T</td>
<td>Reference Product-R</td>
<td>Ratio (T/R) %</td>
<td></td>
<td></td>
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<tr>
<td>lnC&lt;sub&gt;max&lt;/sub&gt;</td>
<td>3349.108</td>
<td>3542.847</td>
<td>94.5</td>
<td>86.27 - 103.59</td>
<td>72.58 - 137.77</td>
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<tr>
<td>lnAUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>41930.709</td>
<td>43788.864</td>
<td>95.8</td>
<td>88.55 - 103.55</td>
<td>80.00 - 125.00</td>
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<tr>
<td>lnAUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>43519.487</td>
<td>45460.151</td>
<td>95.7</td>
<td>88.85 - 103.15</td>
<td>N/AP</td>
</tr>
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</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from zero to t hours
AUC<sub>0-∞</sub> area under the plasma concentration-time curve from zero to ∞ hours
C<sub>max</sub> maximum plasma concentration

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for trospium 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 Trospium chloride 20mg film-coated tablets (Lucis Pharma Limited), is bioequivalent to the reference product Regurin 20 mg coated tablets (Meda Pharmaceuticals Ltd, UK).

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

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

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.
In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MHRA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.
IV.7 **Discussion on the clinical aspects**
The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

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 product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with trospium chloride is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product and its risk-benefit balance is considered similar and 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 this medicine is presented below:
Braile text reads as follows:

**t r o s p i u m**

**c h l o r i d e**

**# 2 0 m g**

**f i l m - c o a t e d**

**t a b l e t s**

*(each box contains 24 tablets)*

Note: dies comply with Marturp Medium cell dimensions.
Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<tr>
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<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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