Public Assessment Report

Decentralised Procedure

Trospium Chloride 20mg Film-Coated Tablets

UK/H/4220/001/DC
UK licence no: PL 17507/0099

Auden Mckenzie Limited
LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Auden Mckenzie Limited a Marketing Authorisation (licence) for the medicinal product Trospium Chloride 20mg Film-Coated Tablets. This medicine is available on prescription only.

Trospium Chloride 20mg Film Coated Tablets are used to treat the symptoms of overactive bladder conditions. For example, needing to go to the toilet frequently, needing to suddenly rush to the toilet and/or having difficulty getting there in time and wetting yourself.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Trospium Chloride 20mg Film-Coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
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Module 2
Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Trospium Chloride 20mg Film-Coated Tablets (PL 17507/0099) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Trospium Chloride 20 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each coated tablet contains 20 mg trospium chloride.

Excipient: Each tablet contains 71 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Coated Tablet.

Yellow, round tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
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).

4.2 Posology and method of administration
One coated tablet twice daily (equivalent to 40 mg of trospium chloride per day).

In patients with severe renal impairment (creatinine clearance between 10 and 30 ml/min/1.73 m²) the recommended dosage is: One coated tablet per day or every second day (equivalent to 20 mg of trospium chloride per day or every second day).

The coated tablet should be swallowed whole with a glass of water before meals on an empty stomach.

The need for continued treatment should be reassessed at regular intervals of 3-6 months.

Since no data are available, use in children under 12 years of age is contra-indicated.

4.3 Contraindications
Trospium chloride is contra-indicated in patients with urinary retention, severe gastro-intestinal condition (including toxic megacolon), myasthenia gravis, narrow-angle glaucoma and tachyarrhythmia.

Trospium chloride is also contra-indicated in patients who have demonstrated hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Trospium chloride should be used with caution by patients:

- with obstructive conditions of the gastro-intestinal tract such as pyloric stenosis
- with obstruction of the urinary flow with the risk of formation of urinary retention
- with autonomic neuropathy
- with hiatus hernia associated with reflux oesophagitis
- in whom fast heart rates are undesirable e.g. those with hyperthyroidism, coronary artery disease and congestive heart failure.
As there are no data in patients with severe hepatic impairment, treatment of these patients with trospium chloride is not recommended. In patients with mild to moderate liver impairment caution should be exercised.

Trospium chloride is mainly eliminated by renal excretion. Marked elevations in the plasma levels have been observed in patients with severe renal impairment. Therefore in this population but also in patients with mild to moderate renal impairment caution should be exercised (see 4.2).

Before commencing therapy organic causes of urinary frequency, urgency, and urge incontinence, such as heart diseases, diseases of the kidneys, polydipsia, or infections, or tumours of urinary organs should be excluded.

Trospium Chloride tablets contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions:

The following potential pharmacodynamic interactions may occur: Potentiation of the effect of drugs with anticholinergic action (such as amantadine, tricyclic antidepressants), enhancement of the tachycardic action of β-sympathomimetics; decrease in efficacy of pro-kinetic agents (e.g. metoclopramide).

Since trospium chloride may influence gastro-intestinal motility and secretion, the possibility cannot be excluded that the absorption of other concurrently administered drugs may be altered.

Pharmacokinetic interactions:

An inhibition of the absorption of trospium chloride with drugs like guar, cholestyramine and colestipol cannot be excluded. Therefore the simultaneous administration of these drugs with trospium chloride is not recommended.

Metabolic interactions of trospium chloride have been investigated in vitro on cytochrome P450 enzymes involved in drug metabolism (P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4). No influence on their metabolic activities were observed. Since trospium chloride is metabolised only to a low extent and since ester hydrolysis is the only relevant metabolic pathway, no metabolic interactions are expected.

4.6 Pregnancy and lactation

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. In rats, placental transfer and passage into the maternal milk of trospium chloride occurs.

For Trospium Chloride 20 mg tablets no clinical data on exposed pregnancies are available.

Caution should be exercised when prescribing to pregnant or breast-feeding women.

4.7 Effects on ability to drive and use machines

Principally, disorders of accommodation can lower the ability to actively participate in road traffic and to use machines.

However, examinations of parameters characterising the ability to participate in road traffic (visual orientation, general ability to react, reaction under stress, concentration and motor coordination) have not revealed any effects of trospium chloride.

4.8 Undesirable effects

Undesirable effects observed with trospium chloride such as dry mouth, dyspepsia and constipation mainly reflect the typical anticholinergic properties of the active ingredient.

In Phase-III clinical studies, dry mouth was very common and occurred in approximately 18% of patients treated with trospium chloride and in approximately 6% treated with placebo (total of 1931 patients of which 911 received placebo).
The following table lists possibly related drug reactions reported for patients treated with Trospium Chloride 20 mg Film-Coated Tablets:

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*These adverse effects occurred mostly in elderly patients and can be facilitated by neurological diseases and/or concomitant intake of other anticholinergic drugs (see section 4.5).

4.9 Overdose
After the administration of a maximum single dose of 360 mg trospium chloride to healthy volunteers, dryness of the mouth, tachycardia and disorders of micturition were observed to an increased extent. No manifestations of severe overdosage or intoxication in humans have been reported to date. Increased anticholinergic symptoms are to be expected as signs of intoxication.

In the case of intoxication the following measures should be taken:

- gastric lavage and reduction of absorption (e.g. activated charcoal)
- ocal administration of pilocarpine to glaucoma patients
- catheterisation in patients with urinary retention
- treatment with a parasympathomimetic agent (e.g. neostigmine) in the case of severe symptoms
- administration of beta blockers in the case of insufficient response, pronounced tachycardia and/or circulatory instability (e.g. initially 1 mg propranolol intravenously along with monitoring of ECG and blood pressure).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Urinary Antispasmodic, ATC code G04BD15.

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.

In two specific safety studies in healthy volunteers trospium chloride has been proven not to affect cardiac repolarisation, but has been shown to have a consistent and dose dependent heart rate accelerating effect.

A long term clinical trial with trospium chloride 20 mg bid found an increase of QT > 60 ms in 1.5% (3/197) of included patients. The clinical relevance of these findings has not been established. Routine safety monitoring in two other placebo-controlled clinical trials of three months duration do not support such an influence of trospium chloride. In the first study an increase of QTcF >= 60 msec was seen in 4/258 (1.6%) in trospium-treated patients versus 9/256 (3.5%) in placebo-treated patients. Corresponding figures in the second trial were 8/326 (2.5%) in trospium-treated patients versus 8/325 (2.5%) in placebo-treated patients.

5.2 Pharmacokinetic properties
After oral administration of trospium chloride maximum plasma levels are reached at 4-6 hours. Following a single dose of 20 mg the maximum plasma level is about 4 ng/ml. Within the tested interval, 20 to 60 mg as a single dose, the plasma levels are proportional to the administered dose. The absolute bioavailability of a single oral dose of 20 mg of trospium chloride (1 coated tablet Trospium Chloride 20 mg tablets) is 9.6 ± 4.5% (mean value ± standard deviation). At steady state the intra-individual variability is 16%, the inter-individual variability is 36%.

Simultaneous intake of food, especially high fat diets, reduces the bioavailability of trospium chloride. After a high-fat meal mean Cmax and AUC are reduced to 15-20% of the values in the fasted state.

Trospium chloride exhibits diurnal variability in exposure with a decrease of both Cmax and AUC for evening relative to morning doses.

Most of the systemically available trospium chloride is excreted unchanged by the kidneys, though a small portion (10% of the renal excretion) appears in the urine as the spiroalcohol, a metabolite formed by ester hydrolysis. The terminal elimination half-life is in the range of 10-20 hours. No accumulation occurs. The plasma protein binding is 50-80%.

Pharmacokinetic data in elderly patients suggests no major differences. There are also no gender differences.

In a study in patients with severe renal impairment (creatinine clearance 8-32 ml/min) mean AUC was 4-fold higher, Cmax was 2-fold higher and the mean half-life was prolonged 2-fold compared with healthy subjects.
Pharmacokinetic results of a study with mildly and moderately hepatically impaired patients do not suggest a need for dose adjustment in patients with hepatic impairment, and are consistent with the limited role of hepatic metabolism in the elimination of trospium chloride.

5.3 Preclinical safety data
Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize starch
Lactose monohydrate
Microcrystalline cellulose
Povidone K30
Sodium starch glycolate
Magnesium stearate

Film-Coat:
Macrogol 400
Hypromellose
Iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC foiled aluminium blister.

Packs of 20 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17507/0099

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/04/2011

10 DATE OF REVISION OF THE TEXT
20/04/2011
Module 3
PATIENT INFORMATION LEAFLET

TROPSIUM CHLORIDE 20mg FILM-COATED TABLETS

Read all of this leaflet carefully because it contains important information for you.

1. What is Tropism Chloride and what is it used for?

The name of this medicine is Tropism Chloride 20mg Film-Coated Tablets. Tropism Chloride 20mg Film-Coated Tablets are used to treat the symptoms of irritable bowel conditions. For example, needing to go to the toilet frequently, needing to suddenly rush to the toilet and/or finding difficulty getting to the toilet and waiting there.

2. Before you take Tropism Chloride

Do not take Tropism Chloride if your doctor has told you that you have:

- An allergic reaction to Tropism Chloride
- Hypersensitivity (an allergic reaction) to any of the ingredients listed in section 6. For allergic reactions, nausea, diarrhoea or intolerance of any tablets
- Urinary retention or chronic obstructive pulmonary disease (COPD)
- The eye condition glaucoma
- Abnormal fluid retention or abnormal heart beats
- Myasthenia gravis (a disorder which causes weakness of muscles)
- A severe gastro-intestinal condition, such as bowel obstruction

Do NOT give this product to children under 12 years of age.

Special Precautions

Check with your doctor or pharmacist before taking this medicine if you suffer from any of the following:

- Any type of ulcer or bowel obstruction
- Blockage of the urinary tract
- Bladder cancer or bladder stones
- Hypersensitivity to any of the ingredients listed in section 6
- Any heart conditions, such as coronary artery disease or congestive heart failure
- Any liver problems
- Any kidney problems

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking this medicine.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Taking some medicines together can be harmful.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:

- Antidepressant (used to treat the symptoms of Parkinson’s disease and as protection against reinfection)
- Tyramine (used to treat the symptoms of Parkinson’s disease)
- A sympathomimetic (one of a class of drugs which can increase the heart rate)
- Metoclopramide (a drug which increases the rate of movement of the digestive tract through your gastric/duodenal system)
- Clozapine (sometimes used in a drug combination)
- Tricyclic antidepressants or sedatives drugs used to reduce the levels of certain substances in your bloodstream

If you are unsure of the types of medicines you are taking, ask your doctor or pharmacist.

Pregnancy and breast feeding

If you are pregnant or breast feeding talk to your doctor before taking Tropism Chloride.

Driving and using machines

Tropism Chloride does not affect your ability to drive or use machines.

Important information about some of the ingredients of Tropism Chloride

This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, please consult your doctor before taking this medicinal product.

3. How to take Tropism Chloride

Always take this medicine exactly as your doctor or pharmacist has told you. The usual dose is once daily before breakfast. Tropism Chloride 20mg Film-Coated Tablets are available in 10 tablets.

Adults and children 12 years or over:
The usual adult dose is 1 tablet every 24 hours. Dosing may be reduced in patients with impaired renal function, elderly patients or patients with hepatic impairment. Dosing may be individualised on an individual basis.

If you forget to take Tropism Chloride:

Take the dose as soon as you remember to take it and then continue on as before. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Tropism Chloride can have side effects, although not everybody gets them. The side effects occurring most frequently are typical for this kind of medicine and comprise:

- Nausea
- Abdominal cramps
- Reduced appetite
- Diarrhoea
- Weight loss

If any of the side effects is severe or lasts more than a few days, or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing Tropism Chloride

Keep all medicines out of the reach and sight of children.

Do not use Tropism Chloride after the expiry date on the blister and blister packs.

The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These resources will help to protect the environment.

6. Further information

What Tropism Chloride contains

Each blister pack contains 20mg of Tropism Chloride as the active ingredient.

The tablets also contain maize starch, lactose monohydrate, microcrystalline cellulose, magnesium stearate, magnesium silicate and cross-linked yellow (E172).

What Tropism Chloride looks like and contents of the pack:

Tropism Chloride tablets are available in boxes of 20 or 50 tablets. Not all pack sizes may be marketed.

Marketing authorisation holder:

Adeleal McElroy (Pharma Clear) Limited

Address:

Bury Street

Road Town

KPI TLL, UK

Representatives:

Telesys BV

Deventerstraat 2

3281 UU (Old Bussum) Netherlands

This leaflet was last approved in February 2012.

For information in large print, on tape, on CD or in Braille, phone

+44 (0)1995 627 429.

Module 3 cont...
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
On 7th April 2011, Ireland and the UK agreed to grant a Marketing Authorisation (MA) to Auden Mckenzie Limited for the medicinal product Trospium Chloride 20mg Film-Coated Tablets. The MA was granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/4220/001/DC). After the national phase, an MA was granted in the UK on 20th April 2011 (PL 17507/0099). This product is a prescription-only medicine.

This is an abridged application for Trospium Chloride 20mg Film-Coated Tablets submitted under Article 10.1 of 2001/83 EC, as amended. This application refers to the reference medicinal product Regurin 20mg Tablets first authorised in Germany on 18th August 1999 to Madaus AG. The reference product has since been granted in all EU countries via the Mutual Recognition procedure; a licence was granted in the UK to Madaus AG (PL 04638/0013) on 14th April 2011. The reference product has since undergone a change of ownership and is currently licensed to Madaus GmbH (PL 25843/0002). The reference product has been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired.

Trospium chloride is a quaternary ammonium compound, which is a competitive antagonist at muscarinic cholinergic receptors.

Trospium chloride is given orally, 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).

No new preclinical or clinical studies were conducted and none are required for this application, which is acceptable given that the application is for a generic version of a product that have been licensed for over 10 years.

This application is supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Trospium Chloride 20mg Film-Coated Tablets, to that of the reference product, Regurin 20mg Tablets (Madaus GmbH, Germany). This study is described in the Clinical Aspects section. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories)
as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is not a generic version of an approved product and it is not likely to change total market of trospium chloride.

II. ABOUT THE PRODUCT

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III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. ACTIVE SUBSTANCE

General Information
Nomenclature
INN: Trospium Chloride
Structure

![Chemical Structure](image)

Chemical name: azonia-3-α-benziloyloxy-8-spiro-1′-pyrrolidinium chloride

Molecular formula: $\text{C}_{25}\text{H}_{30}\text{ClN}_3$  
Molecular weight: 428.00

Description: White or almost white crystalline powder.
Solubility: Soluble in water, freely soluble in methanol and practically insoluble in methylene chloride.

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

DRUG PRODUCT
Description & Composition
Trospium Chloride 20mg Film-Coated Tablets are presented as yellow, round tablets containing 20mg of the active substance, trospium chloride.

Other ingredients consist of pharmaceutical excipients, maize starch, lactose monohydrate, microcrystalline cellulose, povidone K30, sodium starch glycolate and magnesium stearate making up the tablet core; and macrogol 400, hypromellose and iron oxide yellow (E172) making up the film coating.

All excipients used comply with their respective European Pharmacopoeial monograph with the exception of iron oxide yellow (E172) which is controlled to in-house specifications. Satisfactory certificates of analysis have been provided for all excipients. Appropriate justification for the inclusion of each excipient has been provided.

With the exception of lactose monohydrate none of the excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption.
There are no novel excipients used.

**Pharmaceutical development**
A detail of the pharmaceutical development of the medicinal product has been supplied and is satisfactory. The objective was to develop robust, stable, generic formulation, bioequivalent to the innovator product Regurin 20mg Tablets (44545.00.00) initially licensed to Madaus AG in Germany on 18th August 1999.

Comparative dissolution and impurity profiles were provided for test and reference products and were found to be similar.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. The validation data demonstrated consistency of the manufacturing process.

**Finished Product Specification**
Finished product specifications are provided for both release and shelf-life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**
The finished product is packaged in blister strips composed of polyvinylchloride (PVC) with a foiled aluminium lid, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 20 and 60 tablets. The MA Holder (MAH) has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set, with no special storage conditions required for this medicinal product.

**Bioequivalence Study**
A bioequivalence study was presented comparing the test product, Trospium Chloride 20mg Film-Coated Tablets, to the reference product; Regurin 20mg Tablets (Madaus GmbH, Germany).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.
**Expert Report**
A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

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.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application.

**III.2 Non clinical aspects**
The pharmacological, pharmacokinetic and toxicological properties of trospium chloride are well-known. As trospium chloride is a widely used, well-known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review is thus appropriate. An adequate overview has been written by a suitably qualified person.

There are no objections to the approval of trospium chloride from a non-clinical point of view.

**III.3 Clinical aspects**

**Pharmacokinetics**
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

**Study 1**
Single blind, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bio-availability study of Trospium Chloride 20 mg Tablets (test product) and the reference product; Regurin 20mg Tablets (Madaus GmBH, Germany) was carried out in healthy, adult, male human subjects under fasting conditions.

The study was conducted in compliance with Good Clinical Practice (ICH-GCP) and Good Laboratory Practice.

**Study design**
A single dose of the investigational products (1 tablet of 20mg) was administered orally to each subject in each period with 240 ml of water after an overnight fast of 10 hours. A washout period of 10 days was maintained between the two dosing days in each group.

Serial blood sampling before dosing and up to 120 hours after drug administration was carried out in each group.
The plasma samples were assayed for trospium chloride by a validated LC-MS/MS method. The primary variables analysed were: $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ and the secondary variable were $T_{\text{max}}$, $t_{1/2}$, $K_{\text{el}}$.

**Statistical methods**
Pharmacokinetic parameters were calculated by non-compartmental analysis. The peak level ($C_{\text{max}}$) and time to reach peak level ($T_{\text{max}}$) were estimated from the plasma concentration time profile data. The elimination rate constant ($K_{\text{el}}$) was estimated by linear regression of the terminal part of the log-concentration-time curve. The area under the plasma concentration-time curve ($AUC_{0-t}$) was determined by the linear trapezoidal rule, and extrapolated to infinity ($AUC_{0-\infty}$) by dividing the last measurable concentration by the elimination rate constant ($K_{\text{el}}$). $T_{1/2}$ (elimination or terminal half-life) was calculated as $0.693/K_{\text{el}}$.

**Results**
Table: 1 Pharmacokinetic parameters for Trospium (log-transformed geometric means).

<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>
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<td>Test (T)</td>
<td>Reference (R)</td>
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<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>3.0615</td>
<td>2.9728</td>
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<tr>
<td>$AUC_{0-t}$ (ng hr/mL)</td>
<td>34.3719</td>
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<tr>
<td>$AUC_{0-\infty}$ (ng hr/mL)</td>
<td>37.5121</td>
<td>36.0812</td>
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The 90% confidence intervals for $C_{\text{max}}$ and $AUC$ were within the pre-defined acceptance criteria of (80-125%). Bioequivalence has been shown for the test formulation (Trospium Chloride 20mg Film-Coated Tablets) and the reference formulation (Regurin 20mg tablets – Madaus GmbH) under fasting conditions.

**Conclusion**
Based on the submitted bioequivalence study Trospium Chloride 20mg Film-Coated Tablets are considered bioequivalent with Regurin 20mg tablets.

**Pharmacodynamics**
No new pharmacodynamic data have been submitted and none are required for this application.

**Clinical efficacy**
No new efficacy data have been submitted and none are required for this application.

**Clinical safety**
No new safety data have been submitted and none are required for this application.

No deaths were reported during the study. Most of the adverse events reports during the study were mild in intensity and were resolved.
BENEFIT RISK ASSESSMENT
The benefit-risk ratio is considered favourable.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with those for the reference product and is acceptable.

Product Information Leaflet (PIL)
The final wording for the PIL is in line with the approved SmPC and is satisfactory.

Labelling
The labelling is satisfactory.

Expert Report
A satisfactory clinical over view is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

CONCLUSIONS
There are no objections to the approval of this product from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Trospium Chloride 20mg Film-Coated Tablets 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.

No new preclinical data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Trospium Chloride 20mg Film-Coated Tablets and the reference product, Regurin 20mg tablets (Madaus GmbH, Germany).

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with trospium chloride considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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