Safeguarding public health

MHRA

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.

TABLE OF CONTENTS

Module 1

Product Name	Trospium Chloride 20mg film-coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Trospium Chloride
Form	Film-coated tablets
Strength	20 mg
MA Holder	Auden Mckenzie Limited
RMS	UK
CMS	Ireland
Procedure Number	UK/H/4220/001/DC
Timetable	Day 210 – 7th April 2011

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 m^2) 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:

	Very common (>1/10)	Common (≥1/100,<1/10)	Uncommon (≥1/1000, <1/100)	Rare (≥1/10.000, <1/1000)	Very Rare (<1/10.000)	Not known (cannot be estimated from the available data)
Cardiac disorders			Tachycardia			Tachyarrhythmia
Nervous system disorders			Headache	Dizziness		Hallucination* confusion* agitation*
Eye disorders				Vision disorders		
Respiratory, thoracic and mediastinal disorders						Dyspnoea
Gastrointestinal disorders	Dry mouth	Dyspepsia Constipation Abdominal pain Nausea	Flatulence Diarrhoea			
Renal and urinary disorders				Micturition disorders Urinary retention		
Skin and subcutaneous disorders				Rash	Angio-oedema	Pruritus Urticaria Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
Muscoskeletal and connective tissue disorders				Myalgia Arthralgia		
General disorders and administration site conditions			Chest pain			Asthenia
Immune system disorders						Anaphylaxis
Investigations						Mild to moderate increase in serum transaminase levels

*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 M_1-, M_2- and M_3-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 gastro-intestinal and genito-urinary tract.

Furthermore, it can inhibit the secretion of bronchial mucus, saliva, sweat and the occular 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 4ng/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 C_{max} 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 C_{max} 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 8-32ml/min) mean AUC was 4-fold higher, C_{max} 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

PACKAGE LEAFLET

PATIENT INFORMATION LEAFLET

TROSPIUM CHLORIDE 20MG FILM-COATED TABLETS

Read all of this leaflet carefully because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

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

The name of this medicine is Trospium Chloride 20 mg Film-Coated Tablets. Trospium Chloride 20 mg 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.

2. Before you take Trospium Chloride

Do not take Trospium Chloride if your doctor has told you that you have:
- An allergic reaction to Trospium Chloride or any of the ingredients listed in section 6. (An allergic reaction can be a rash, itchiness or shortness of breath).
- Urinary retention i.e. urination occurs less frequently than normal.
- The eye condition glaucoma.
- Abnormal/faster than normal heart beats.
- Myasthenia gravis (a disorder which causes muscle fatigue).
- A severe gastro-intestinal condition, such as toxic megacolon.

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

Special Precautions
Check with your doctor or pharmacist before taking your medicine if you suffer from any of the following:
- Any type of stomach or bowel obstruction.
- Blockage of the urinary tract.
- Neuropathy i.e. nerve damage.
- A hiatus hernia associated with reflux oesophagitis. This is usually associated with heartburn which worsens on bending or lying down.
- An overactive thyroid.
- 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:
- Amantadine (used in the treatment of Parkinson's disease or as protection against influenza).
- Tricyclic antidepressants.
- A 'sympathomimetic' (one of a class of drugs which can increase the heart rate).
- Metoclopramide (a drug which increases the rate of movement of digested food through your gastro-intestinal system).
- Guar gum (sometimes used in a type of diabetes).
- Cholestyramine or colestipol (drugs used to reduce the levels of certain fats 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 Trospium Chloride.

Driving and using machines
Trospium Chloride does not affect your ability to drive or use machines.

Important information about some of the ingredients of Trospium Chloride
This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, please contact your doctor before taking this medicinal product.

3. How to take Trospium Chloride

Always take this medicine exactly as your doctor or pharmacist has told you. You should check with them if you are not sure. Trospium Chloride should be taken orally.

Adults and children 12 years or over:
The usual dose for adults is one tablet twice a day. Doctors may prescribe different doses to this. For example, patients with kidney problems may take a reduced dose of one tablet per day or one tablet every second day.
Read the pharmacist's label it will tell you exactly how many you should take.

The tablets should be swallowed whole with a glass of water, **before meals** on an empty stomach.

If symptoms persist, contact your doctor or pharmacist. Your doctor will want to **assess your treatment every 3 to 6 months**, to decide whether this medicine is the best one for you.

continued... please turn over

Children under 12 years of age:
This product should not be taken by children under 12 years of age.

If you take more Trospium Chloride than you should:
It is always important to follow the recommended dose on the label. If too many tablets are taken by accident, contact your doctor or hospital immediately.

If you forget to take Trospium 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, Trospium 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 of dry mouth, dyspepsia and constipation.

To give you an idea of how many patients might get side effects, they have been listed as very common, common, uncommon, rare, very rare and other side effects. These mean the following:

Very common	More than 1 in 10 people.
Common	Up to 1 in 10 people.
Uncommon	Up to 1 in 100 people.
Rare	Up to 1 in 1,000 people.
Very rare	Fewer than 1 in 10,000 people.
Other side effects	The frequency is not known.

The following side effects below are serious and will require immediate action if you experience them. You should **stop taking Trospium Chloride and see your doctor immediately** if the following symptoms occur:
- Swelling of the face, tongue and windpipe which can cause great difficulty in breathing (affects less than 1 user in 10,000).
- A sudden allergic reaction with shortness of breath, rash, wheezing, and drop of blood pressure (frequency unknown).
- Serious reactions with severe blistering and peeling of the skin and/or mucous membranes like for example in the lips, eyes, mouth, nose and genitals. This may be accompanied by a fever and chills, aching muscles and generally feeling unwell (frequency unknown).

Less serious side effects:

Very Common:
- Dry mouth

Common:
- Constipation
- Nausea
- Abdominal pain
- Indigestion (dyspepsia)

Uncommon:
- Fast heart rate (tachycardia)
- Headache
- Flatulence
- Diarrhoea
- Chest pain

Rare:
- Dizziness
- Difficulty emptying the bladder
- Urinary retention
- Difficulty seeing objects close-up
- Rash
- Joint and muscle pains

Other Side Effects:
- Accelerated and irregular heart rate (tachyarrhythmia)
- Difficulty in breathing
- Itchiness
- Nettle rash (hives)
- General feeling of weakness (asthenia)
- Slight to moderate increase of certain liver enzyme levels
- Sporadic cases of hallucination, confusion and agitation have occurred mostly in elderly patients and can be facilitated by neurological diseases and/or other drugs with a similar mechanism of action taken at the same time

If any of the above side effects are troublesome or last 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 Trospium Chloride

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

Do not use Trospium Chloride after the expiry date on the carton and blister.
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 measures will help to protect the environment.

6. Further Information

What Trospium Chloride contains:
Each coated tablet contains 20 mg of Trospium Chloride as the active ingredient.

The tablets also contain maize starch, lactose monohydrate, microcrystalline cellulose, povidone K30, sodium starch glycolate, magnesium stearate, macrogol 400, hypromellose and iron oxide yellow (E172).

What Trospium Chloride looks like and contents of the pack:
Trospium Chloride tablets are round yellow tablets.

Trospium Chloride tablets are available in boxes of 20 or 60 tablets. Not all pack sizes may be marketed.

Marketing authorisation holder:
Auden Mckenzie (Pharma Division) Ltd.
Mckenzie House
Bury Street
Ruislip, Middlesex
HA4 7TL, UK

Manufacturer:
Tiofarma BV
Benjamin Franklinstraat 9
3261 LW Oud-Beijereland
Netherlands

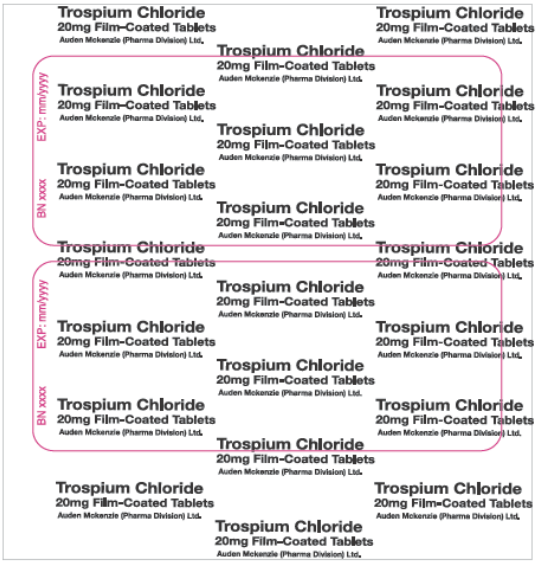
This leaflet was last approved in February 2011.

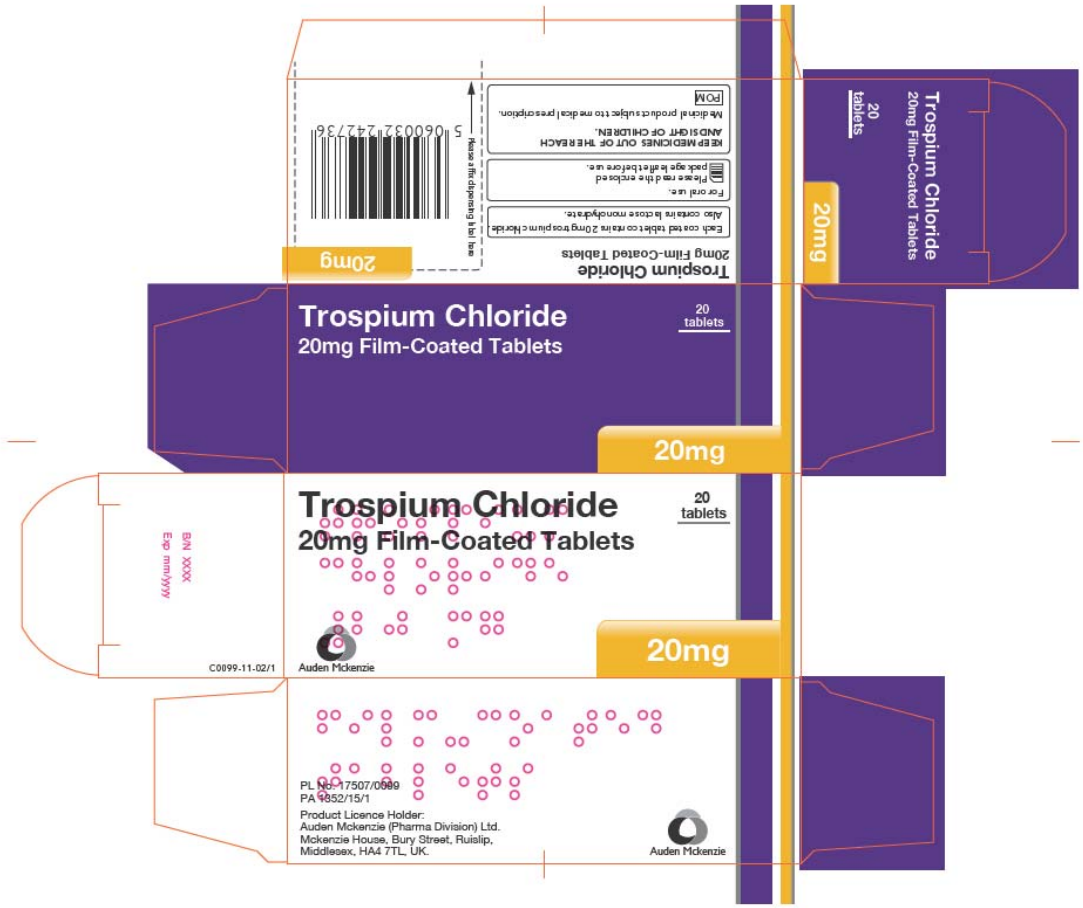
For information in large print, on tape, on CD or in Braille, phone +44 (0)1895 627 420.

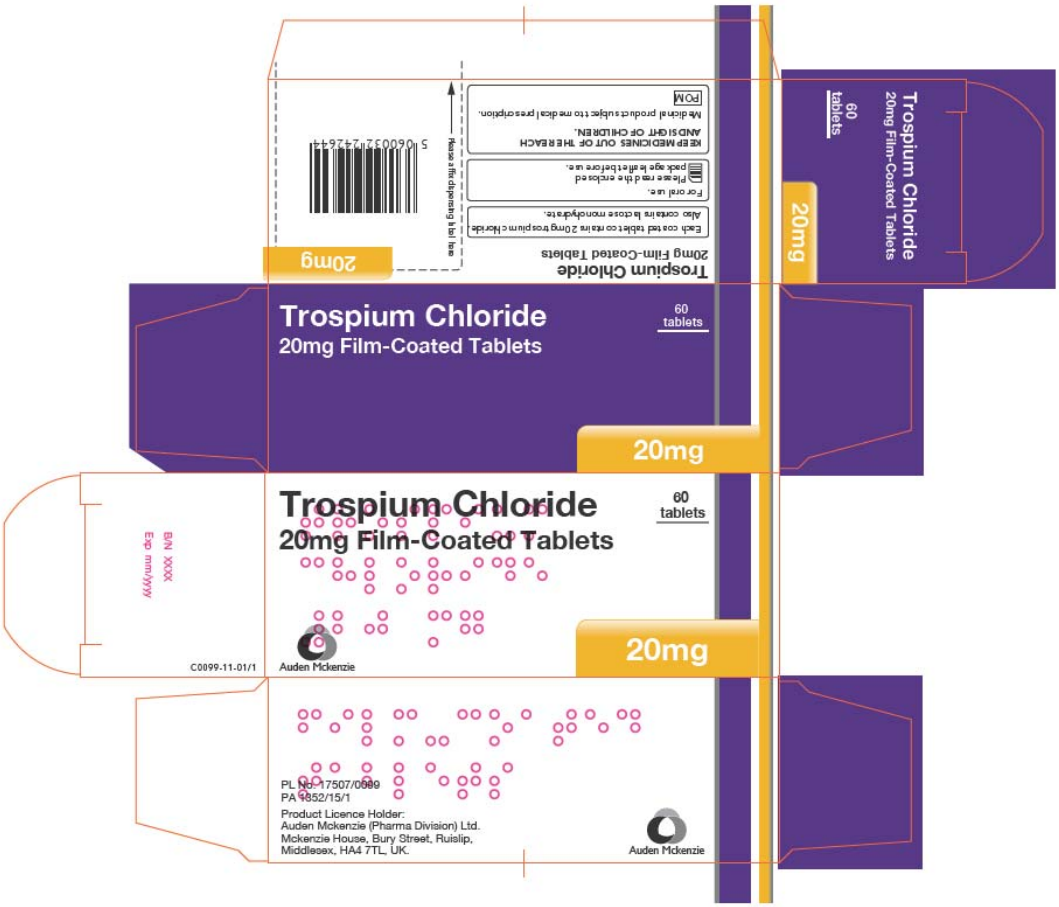
P099-10-01/1

Auden Mckenzie

Module 4
Labelling






Trospium Chloride
20mg Film-Coated Tablets
60 tablets
20mg
B/N XXXX
Exp mm/yyyy
C0099-11-01/1
Auden Mckenzie
PL No 17507/0089
PA 4852/15/1
Product Licence Holder:
Auden Mckenzie (Pharma Division) Ltd.
Mckenzie House, Bury Street, Ruislip,
Middlesex, HA4 7TL, UK.

Module 5
Scientific discussion during initial procedure

I 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.

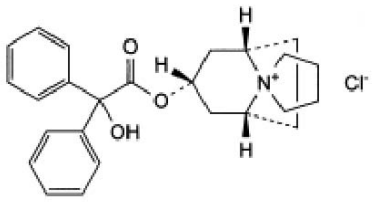
The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is not a generic version of an approved product and it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

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Trospium Chloride 20mg film-coated Tablets
Name(s) of the active substance(s) (INN)	Trospium Chloride
Pharmacotherapeutic classification (ATC code)	G04 BD09 Urinary antispasmodics
Pharmaceutical form and strength(s)	20mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/4220/01/DC
Reference Member State	United Kingdom
Member States concerned	Ireland
Marketing Authorisation Number(s)	PL 17507/0099
Name and address of the authorisation holder	Auden Mckenzie (Pharma Division) Ltd Mckenzie House, Bury Street, Ruislip, Middlesex, UK HA4 7TL

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

General Information
Nomenclature
INN: Trospium Chloride
Structure



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

Molecular formula: $C_{25}H_{30}ClN0_3$

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 as 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: Cmax, AUC0-t and AUC0-∞ and the secondary variable were Tmax, t1/2, Kel.

Statistical methods

Pharmacokinetic parameters were calculated by non-compartmental analysis. The peak level (C_{max}) and time to reach peak level (T_{max}) were estimated from the plasma concentration time profile data. The elimination rate constant (K_{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-}) by dividing the last measurable concentration by the elimination rate constant (K_{el}). $T_{1/2}$ (elimination or terminal half-life) was calculated as $0.693/K_{el}$.

Results

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

Table 1 : Geometric Least Squares Mean, Ratios and 90 % Confidence Interval for Primary Pharmacokinetic Parameters of Trospium

Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test (T)	Reference (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	3.0615	2.9728	102.98	92.75	114.34
AUC_{0-t} (ng.hr/mL)	34.3719	32.7516	104.95	96.11	114.59
$AUC_{0-\infty}$ (ng.hr/mL)	37.5121	36.0812	103.97	96.03	112.56

The 90% confidence intervals for C_{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

Date submitted	Application type	Scope	Outcome