PRODUCT MONOGRAPH

[Pr]ACCEL-TROSPIUM

Trospium Chloride Tablets

20 mg

House Standard

ATC G04BD09

Antispasmodic

Accel Pharma Inc.
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PrACCEL-TROSPIUM

Trospium Chloride Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	coated tablet / 20 mg	Croscarmellose sodium, hypromellose, iron oxide yellow, magnesium stearate, maltodextrin, medium chain triglycerides, microcrystalline cellulose, polydextrose, povidone, talc, titanium dioxide

INDICATIONS AND CLINICAL USE

ACCEL-TROSPIUM (trospium chloride) is indicated for:

- the treatment of overactive bladder with symptoms of urge or mixed urinary incontinence, urgency, and urinary frequency.

CONTRAINDICATIONS

ACCEL-TROSPIUM is contraindicated in patients:

- with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions:
- who have demonstrated hypersensitivity to the drug, its ingredients, or any component of the container. For a complete listing, see "**DOSAGE FORMS, COMPOSITION AND PACKAGING**".

WARNINGS AND PRECAUTIONS

General

Patients should be informed that anticholinergic agents, such as trospium chloride, may produce clinically significant adverse effects related to anticholinergic pharmacological activity. For example, heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as trospium chloride are used in a hot environment. Because anticholinergics such as trospium chloride may also produce dizziness or blurred vision, patients should be advised to exercise caution. Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents.

Gastrointestinal

ACCEL-TROSPIUM should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see "**CONTRAINDICATIONS**"). ACCEL-TROSPIUM, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony and myasthenia gravis.

Ophthalmologic

In patients being treated for narrow-angle glaucoma, ACCEL-TROSPIUM should only be used if the potential benefits outweigh the risks and in that circumstance only with careful monitoring.

Cardiovascular

The effect of 20 mg twice daily (bid) and up to 100 mg bid trospium chloride on QT interval was evaluated in a single-blind, randomized, placebo and active (moxifloxacin 400 mg qd) controlled 5 day parallel trial in 170 male and female healthy volunteer subjects aged 18 to 45 years. The QT interval was measured over a 24 hour period at steady state. The 100 mg bid dose of trospium chloride was chosen because this dose achieves the C_{max} expected in severe renal impairment. Trospium chloride was not associated with an increase in individual corrected (QTcI) or Fridericia corrected (QTcF) QT interval at any time during steady state measurement, while moxifloxacin was associated with a 6.4 msec increase in QTcF.

In this study, asymptomatic, non-specific T wave inversions were observed more often in subjects receiving trospium chloride than in subjects receiving moxifloxacin or placebo following five days of treatment. This finding was not observed during routine safety monitoring in two other U.S. placebo-controlled clinical trials in 591 trospium chloride -treated overactive bladder patients (See "**CLINICAL TRIALS**"). The clinical significance of T wave inversion in this study is unknown.

Trospium chloride is associated with an increase in heart rate that correlates with increasing plasma concentrations. In the study described above, trospium chloride demonstrated a mean increase in heart rate compared to placebo of 9.1 bpm for the 20 mg dose and of 18.0 bpm for the 100 mg dose. In the two U.S. placebo-controlled trials in patients with overactive bladder, the mean increase in heart rate compared to placebo in Study 1 was observed to be 3.0 bpm and in Study 2 was 4.0 bpm.

Trospium chloride has not been formally evaluated in patients with conditions such as congestive heart failure, hypokalemia, myocardial infarction, etc., which potentiate proarrhythmic risk.

Caution should be used when prescribing antimuscarinics/anticholinergics to patients with pre-existing cardiac diseases.

Hepatic/Biliary/Pancreatic

Caution should be used when administering ACCEL-TROSPIUM in patients with moderate hepatic dysfunction (see "**ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**"). There is no experience in patients with severe hepatic dysfunction.

Immune

Angioedema of the face, lips, tongue and/or larynx has been reported with trospium chloride. In one case, angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, ACCEL-TROSPIUM should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Renal

ACCEL-TROSPIUM should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Dose modification is recommended in patients with severe renal insufficiency [Clcr 0.25 - 0.5 mL/sec (15 - 30 mL/min)]. In such patients, ACCEL-TROSPIUM should be administered as 20 mg once a day at bedtime (see "**DOSAGE AND ADMINISTRATION**"). The use of trospium chloride in patients with renal function <0.25 mL/sec (15 mL/min) has not been studied.

Sexual Function/Reproduction

No evidence of impaired fertility was observed in rats administered doses up to 200 mg/kg/day (about 10 multiples of the expected clinical exposure via AUC). The effect of trospium chloride on sexual function/reproduction in humans has not been studied.

Special Populations

Pregnant Women: Trospium chloride has been shown to cause maternal toxicity in rats and a decrease in fetal survival in rats administered approximately 10 times the expected clinical exposure (AUC). The no effect levels for maternal and fetal toxicity were approximately equivalent to the expected clinical exposure in rats, and about 5-6 times the expected clinical exposure in rabbits. No malformations or developmental delays were observed. There are no adequate and well controlled studies in pregnant women. ACCEL-TROSPIUM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: Trospium chloride (2 mg/kg po and 50 µg/kg iv) was excreted, to a limited extent (<1%), into the milk of lactating rats. The activity observed in the milk was primarily from the parent compound. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trospium chloride is administered to a nursing woman. ACCEL-TROSPIUM should be used during lactation only if the potential benefit justifies the potential risk to the newborn.

Pediatrics: The safety and effectiveness of trospium chloride in pediatric patients have not been established.

Geriatrics (≥ 75 years of age): Of the 262 patients with overactive bladder who received treatment with trospium chloride in the US 12-week clinical study, 120 patients (45.8%) were 65 years of age

and older. Forty-two trospium chloride -treated patients (16%) were ≥ 75 years of age.

Age did not, independently, affect trospium pharmacokinetics. However, the population older than 75 years has greater heterogeneity with respect to hepatic and renal function and has been shown to have an increased incidence of anticholinergic side effects.

In this study, the incidence of commonly reported anticholinergic adverse events in patients treated with trospium chloride (including dry mouth, constipation, dyspepsia, urinary tract infection (UTI), and urinary retention) was higher in patients 75 years of age and older as compared to younger patients. Therefore, based upon tolerability, the dose frequency of ACCEL-TROSPIUM may be reduced to 20 mg once daily in patients 75 years of age and older.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with trospium chloride were conducted in mice and rats. A 78-week carcinogenicity study in mice and a 104-week carcinogenicity study in rats were conducted at doses of 2, 20, and 200 mg/kg/day. No evidence of a carcinogenic effect was found in either mice or rats. The 200 mg/kg/day dose in the mouse and rat represents approximately 25 and 60 times, respectively, the human dose based on body surface area. At 200 mg/kg/day in the mouse and rat after 4 weeks the AUC was 34 and 753 ngAh/mL, respectively. The exposure in the rat is 8.6-fold higher than the AUC following 40 mg daily exposure in healthy young or elderly subjects (88 ngAh/mL).

Trospium chloride was not mutagenic in tests for detection of gene mutations in bacteria (Ames test) and mammalian cells (L5178Y mouse lymphoma and Chinese Hamster Ovary [CHO] cells) or *in vivo* in the rat micronucleus test.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Trospium chloride antagonizes the effect of acetylcholine on cholinergically innervated organs and exhibits parasympatholytic action by reducing smooth muscle tone, such as in the urogenital and gastrointestinal tracts. Adverse events characteristically associated with the use of anticholinergic agents are dry mouth, constipation, urinary retention, dry eyes, blurred vision, tachycardia, increased heart rate, and palpitation. These adverse effects have been investigated for trospium chloride in animal pharmacology studies and were monitored in human clinical trials.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of trospium chloride was evaluated in Phase 2 and 3 controlled clinical trials in a total of 2975 patients, who were treated with trospium chloride (N = 1673), placebo (N = 1056) or active control medications (N = 246). Of this total, 1181 patients participated in two, twelve-week, Phase 3, US efficacy and safety studies and a 9-month open-label extension. Of this total, 591 patients received trospium chloride 20 mg twice daily. In all controlled trials combined, 232 and 208 patients received treatment with trospium chloride for at least 24 and 52 weeks, respectively.

In all placebo-controlled trials combined, the incidence of serious adverse events was 2.9% among patients receiving trospium chloride 20 mg bid and 1.5% among patients receiving placebo. Of these, 0.2% and 0.3% were judged to be at least possibly related to treatment with trospium chloride or placebo, respectively, by the investigator.

Table 1 lists treatment emergent adverse events from the combined 12-week US safety and efficacy trials that were judged to be at least possibly related to treatment with trospium chloride by the investigator, were reported by at least 1% of patients, and were reported more frequently in the trospium chloride group than in the placebo group.

The two most common adverse events reported by patients receiving trospium chloride 20 mg bid were dry mouth and constipation. The single most frequently reported adverse event for trospium chloride, dry mouth, occurred in 20.1% of trospium chloride treated patients and 5.8% of patients receiving placebo. In the two Phase 3 US studies, dry mouth led to discontinuation in 1.9% of patients treated with trospium chloride 20 mg bid. For the patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

Table 1- Incidence (%) of adverse events judged at least possibly related to treatment with trospium chloride, reported in ≥1% of all patients treated with trospium chloride and more frequent with trospium chloride (20 mg bid) than placebo in Studies 1[1] and 2[2] combined

Adverse Event	Placebo (N=590)	Trospium chloride 20 mg bid (N=591)
Gastrointestinal disorders		
Dry mouth	34 (5.8)	119 (20.1)
Constipation	27 (4.6)	57 (9.6)
Abdominal pain upper	7 (1.2)	9 (1.5)
Constipation aggravated	5 (0.8)	8 (1.4)
Dyspepsia	2 (0.3)	7 (1.2)
Flatulence	5 (0.8)	7 (1.2)
Nervous system disorders		
Headache	12 (2.0)	25 (4.2)
General Disorders		
Fatigue	8 (1.4)	11 (1.9)
Renal and Urinary Disorders		
Urinary retention	2 (0.3)	7 (1.2)
Eye Disorders		
Dry eyes NOS	2 (0.3)	7 (1.2)

Abbreviations: bid = twice daily, NOS = not otherwise specified

Other adverse events from the Phase 3, US placebo-controlled trials judged possibly related to treatment with trospium chloride by the investigator, occurring in ≥0.5% of trospium chloride -treated

patients, and more common with trospium chloride than placebo are: tachycardia NOS, vision blurred, abdominal distension, vomiting NOS, dysgeusia, dry throat, and dry skin.

During controlled clinical studies, one event of angioneurotic edema was reported.

Though not an adverse effect, heart rate was noted to increase by an average of 4 beats per minute in those subjects on active treatment.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Blood and lymphatic system disorders: lymphadenopathy
Cardiac disorders: angina pectoris, coronary artery disease, palpitations, supraventricular extrasystoles, tachycardia
Ear and labyrinth disorders: ear pain
Endocrine disorders: endocrine disorder
Eye disorders: accommodation disorder, dry eye, eye pain, vision blurred
Gastrointestinal disorders: abdominal discomfort, abdominal distension, abdominal pain upper, constipation aggravated, gastrointestinal disorder, mouth ulceration, vomiting
General disorders and administration site conditions: chest pain, influenza like illness, oedema, oedema peripheral, thirst
Infections and infestations: urinary tract infection
Investigations: electrocardiogram abnormal, heart rate increased, QRS axis abnormal, residual urine volume, weight increased
Metabolism and nutrition disorders: appetite decreased, fluid retention, hyperuricaemia
Musculoskeletal and connective tissue disorders: back pain, muscle cramps, pain in jaw, peripheral swelling
Nervous system disorders: dysgeusia, migraine
Renal and urinary disorders: bladder pain, dysuria, haematuria, micturition disorder, micturition urgency, renal pain, urinary hesitation, urine abnormal, urine odour abnormal
Reproductive system and breast disorders: vaginal pain
Respiratory, thoracic and mediastinal disorders: dry throat, hoarseness, nasal dryness, respiratory tract congestion, rhinitis
Skin and subcutaneous tissue disorders: dermatitis contact, dry skin, eczema, hair growth abnormal, photosensitivity reaction, pruritus, rash erythematous, rash, sweating increased, urticaria
Vascular disorders: flushing, hot flushes, orthostatic hypotension

Abnormal Hematologic and Clinical Chemistry Findings

Analysis of laboratory data from 1 clinical pharmacology study and 2 controlled studies did not identify any trends to suggest that trospium chloride is associated with any relevant laboratory abnormalities in hematology, clinical chemistry, or urinalysis parameters.

Post-Market Adverse Drug Reactions

Additional spontaneous adverse events, regardless of relationship to drug, reported from marketing experience with trospium chloride include: gastritis, palpitations, supraventricular tachycardia, chest pain, Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylactic reaction, angioedema,

syncope, myalgia, arthralgia, rhabdomyolysis, vision abnormal, hallucinations*, confusion*, agitation*, delirium, and "hypertensive crisis".

* Hallucinations, confusion, and agitation occurred mostly in elderly patients and can be facilitated by neurological diseases and/or concomitant intake of other anticholinergic drugs (see "**DRUG INTERACTIONS**").

DRUG INTERACTIONS

Overview

Possible drug interactions, based on the anticholinergic properties of trospium chloride, could include potentiation of the anticholinergic action of agents possessing these properties. Also, trospium chloride could theoretically alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

The major route of excretion of trospium chloride is the kidney. Consequently, concomitant drug therapy that significantly interferes with renal excretion of trospium chloride may cause drug- drug interactions (see "**Drug-Drug Interactions**").

Drug-Drug Interactions

The concomitant use of ACCEL-TROSPIUM with other anticholinergic agents that produce dry mouth, constipation, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

No *in vivo* drug-drug interaction studies have been performed to assess the effect of concomitant medications on the pharmacokinetics of trospium chloride or to assess the effect of trospium chloride on the pharmacokinetics of other drugs. Trospium chloride is metabolized by esterases and excreted by the kidneys by a combination of tubular secretion and glomerular filtration. Based on in vitro data, no clinically relevant interactions with the metabolism of trospium chloride are expected. However, drugs which are actively secreted (e.g. digoxin, procainamide, pancuronium, morphine, vancomycin, metformin and tenofovir) may interact with trospium chloride by competing for renal tubular secretion. Coadministration of ACCEL-TROSPIUM with drugs that are eliminated by active renal tubular secretion may increase the serum concentration of trospium chloride and/or the coadministered drug due to competition for this elimination pathway. Careful patient monitoring is recommended in patients receiving such drugs (See "**ACTION AND CLINICAL PHARMACOLOGY, Excretion**").

Drug-Food Interactions

Coadministration of trospium chloride with food has been shown to reduce drug absorption (See "**ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Effect of Food**"). ACCEL-TROSPIUM should therefore be taken at least one hour prior to meals or on an empty stomach (See "**DOSAGE AND ADMINISTRATION**").

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
Interactions between trospium chloride and laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients with severe renal impairment [CLcr 0.25 - 0.5 mL/sec (15 - 30 mL/min)] (See "WARNINGS AND PRECAUTIONS, Renal").
- Geriatric patients ≥75 years of age (See "WARNINGS AND PRECAUTIONS, Special Populations").

Recommended Dose and Dosage Adjustment
The recommended dose is 20 mg twice daily.

Dosage modification is recommended in the following patient populations:

For patients with severe renal impairment [CLcr 0.25 - 0.5 mL/sec (15 - 30 mL/min)], the recommended dose is 20 mg once daily at bedtime. The use of trospium chloride in patients with renal function <0.25 mL/sec (15 mL/min) has not been studied.

In geriatric patients ≥ 75 years of age, dose may be titrated down to 20 mg once daily based upon tolerability (See "WARNINGS AND PRECAUTIONS, Special Populations").

Caution should be used when administering ACCEL-TROSPIUM to patients with moderate or severe hepatic impairment.

Missed Dose
If a dose is skipped, patients are advised to take their next dose on an empty stomach 1 hour prior to their next meal.

Administration
ACCEL-TROSPIUM should be dosed at least one hour before meals or given on an empty stomach.

OVERDOSAGE

Overdosage with ACCEL-TROSPIUM may result in severe anticholinergic effects. Treatment should be supportive and provided according to symptoms. In the event of overdosage, electrocardiographic (ECG) monitoring is strongly recommended.

A 7-month-old baby experienced tachycardia and mydriasis after administration of a single dose of trospium chloride 10 mg given by a sibling. The baby's weight was reported as 5 kg.

Following admission into the hospital and about 1 hour after ingestion of the trospium chloride, medicinal charcoal was administered for detoxification. While hospitalized, the baby experienced mydriasis and tachycardia up to 230 beats/minute. Therapeutic intervention was not deemed necessary. The baby was discharged as completely recovered the following day.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Trospium chloride is an antispasmodic, antimuscarinic agent.

Trospium chloride antagonizes the effect of acetylcholine on muscarinic receptors in cholinergically innervated organs. Its parasympatholytic action reduces the tonus of smooth muscle in the bladder. Receptor assays showed that trospium chloride has negligible affinity for nicotinic receptors as compared to muscarinic receptors at concentrations obtained from therapeutic doses.

Pharmacodynamics

Placebo-controlled studies employing urodynamic variables were conducted in patients with conditions characterized by involuntary detrusor contractions. The results demonstrate that trospium chloride increases maximum cystometric bladder capacity and volume at first detrusor contraction.

Pharmacokinetics

A summary of mean (± standard deviation) pharmacokinetic parameters for a single 20 mg dose of trospium chloride is provided in **Table 2**.

Table 2 - Mean (± SD) Pharmacokinetic Parameter Estimates for a Single 20 mg Trospium Chloride Dose in Healthy Volunteers

C_{max} (ng/mL)	AUC_{0-4} (ng/mL≅hr)	T_{max} (hr)	t_2 (hr)
3.5 ± 4.0	36.4 ± 21.8	5.3 ± 1.2	18.3 ± 3.2

The mean plasma concentration-time (+ SD) profile for trospium chloride is shown in **Figure *1***.

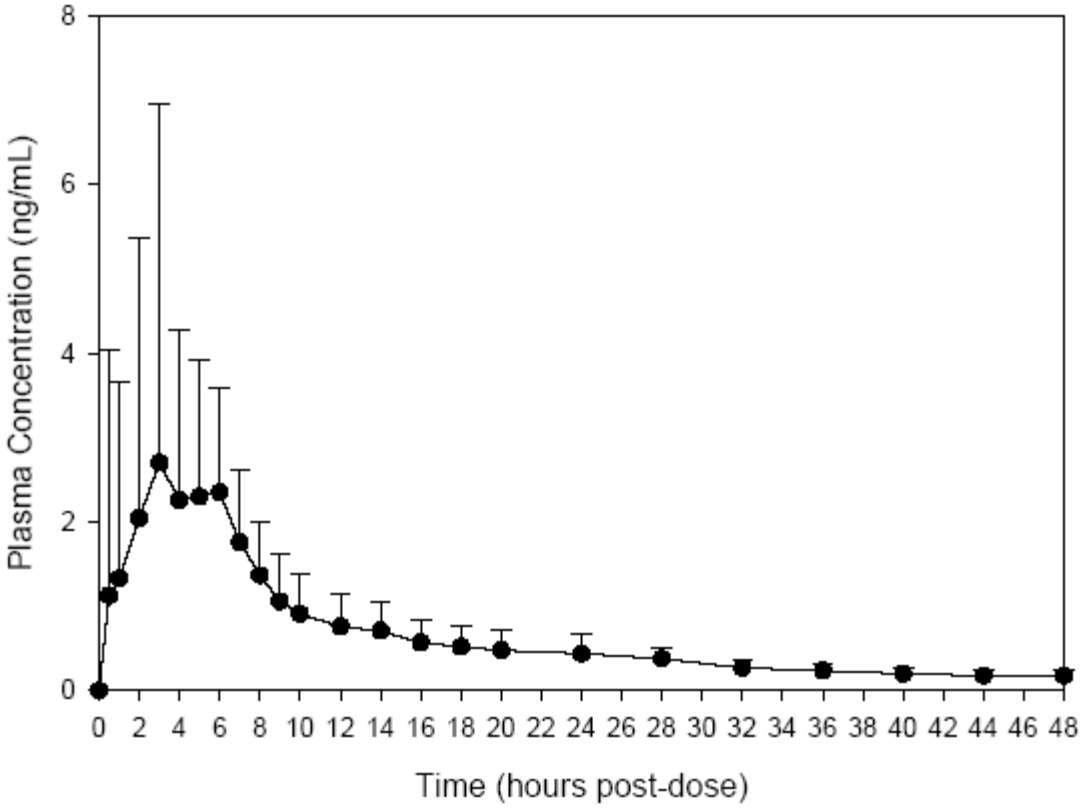


Figure 1 - Mean (+ SD) Concentration-Time Profile for a Single 20 mg Oral Dose of Trospium Chloride in Healthy Volunteers

Absorption: After oral administration, less than 10% of the dose is absorbed. Mean absolute bioavailability of a 20 mg dose is 9.6% (range: 4.0-16.1%). Peak plasma concentrations (C_{max}) occur between 5 to 6 hours post-dose. Mean C_{max} increases greater than dose-proportionally; a 3- fold and 4-fold increase in C_{max} was observed for dose increases from 20 mg to 40 mg and from 20 mg to 60 mg, respectively. AUC exhibits dose linearity for single doses up to 60 mg. Trospium chloride exhibits diurnal variability in exposure with a decrease in C_{max} and AUC of up to 59% and 33%, respectively, for evening relative to morning doses.

Effect of Food: Administration with a high fat meal resulted in reduced absorption, with AUC and C_{max} values 70-80% lower than those obtained when trospium chloride was administered while fasting. Therefore, it is recommended that trospium chloride should be taken at least one hour prior to meals or on an empty stomach. (See "**DOSAGE AND ADMINISTRATION**").

Distribution: Protein binding ranged from 50 to 85% when therapeutic concentration levels (0.5 – 50 ng/mL) were incubated with human serum *in vitro*.

The ^{3}H-trospium chloride ratio of plasma to whole blood was 1.6:1. This ratio indicates that the majority of ^{3}H-trospium chloride is distributed in plasma. The apparent volume of distribution for

a 20 mg oral dose is 395 (∀ 140) liters.

Metabolism: The metabolic pathway of trospium chloride in humans has not been fully defined. Of the 10% of the dose absorbed, metabolites account for approximately 40% of the excreted dose following oral administration. The major metabolic pathway is hypothesized as ester hydrolysis with subsequent conjugation of benzylic acid to form azoniaspironortropanol with glucuronic acid. Cytochrome P450 is not expected to contribute significantly to the elimination of trospium chloride. *In vitro* data from human liver microsomes investigating the inhibitory effect of trospium chloride on seven cytochrome P450 isoenzyme substrates (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4) suggest a lack of inhibition at clinically relevant concentrations of trospium chloride[3].

Excretion: The plasma half-life for trospium chloride following oral administration is approximately 20 hours. After administration of oral ^{14}C-trospium chloride, the majority of the dose (85.2%) was recovered in feces and a smaller amount (5.8% of the dose) was recovered in urine; 60% of the radioactivity excreted in urine was unchanged trospium chloride.

The mean renal clearance for trospium chloride 8 mL/sec (29.07 L/hour) is 4-fold higher than average glomerular filtration rate, indicating that active tubular secretion is a major route of elimination for trospium chloride. There may be competition for elimination with other compounds that are also renally eliminated (See "**DRUG INTERACTIONS**").

Special Populations and Conditions

Pediatrics: The pharmacokinetics of trospium chloride were not evaluated in pediatric patients.

Geriatrics: Age did not appear to significantly affect the pharmacokinetics of trospium chloride however, increased anticholinergic side effects unrelated to drug exposure were observed in patients ≥ 75 years of age. (See "**WARNINGS AND PRECAUTIONS, Special Populations**", and "**DOSAGE AND ADMINISTRATION**").

Gender: Studies comparing the pharmacokinetics in different genders had conflicting results. When a single 40 mg trospium chloride dose was administered to 16 elderly subjects, exposure was 45% lower in elderly females compared to elderly males. When 20 mg trospium chloride was dosed bid for 4 days to 6 elderly males and 6 elderly females (60 to 75 years), AUC and C_{max} were 26% and 68% higher, respectively, in females without hormone replacement therapy than in males.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: There is no information regarding the effect of severe hepatic impairment on exposure to trospium chloride. Maximum trospium chloride concentration (C_{max}) increased 12% and 63% in subjects with mild and moderate hepatic impairment, respectively, compared to healthy subjects. Mean area under the plasma concentration-time curve (AUC) was similar. Caution should be used when administering trospium chloride to patients with moderate and severe hepatic dysfunction. (See "**WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**").

Renal Insufficiency: Severe renal impairment significantly altered the disposition of trospium chloride. A 4.5-fold and 2-fold increase in mean AUC_{0-4} and C_{max}, respectively, and the appearance of an additional elimination phase with a long half-life (– 33 hr) was detected in patients with severe renal insufficiency [Clcr 0.25 - 0.5 mL/sec (15 - 30 mL/min)] compared with healthy, nearly age-matched subjects. The different pharmacokinetic behavior of trospium chloride in patients with severe renal insufficiency necessitates adjustment of dosage frequency. The pharmacokinetics of trospium chloride have not been studied in people with moderate or mild renal impairment [CLcr ranging from 0.5 - 1.3 mL/sec (30-80 mL/min)]. (See "**WARNINGS AND PRECAUTIONS, Renal**", and "**DOSAGE AND ADMINISTRATION**"). The use of trospium chloride in patients with renal function <0.25 mL/sec (15 mL/min) has not been studied.

STORAGE AND STABILITY

Store at controlled room temperature 15° to 30°C.

Keep in a safe place out of reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Pharmaceutical form:
Round, light Yellow-Brown, biconvex coated tablet.

Composition:
Each tablet contains 20 mg of trospium chloride.

Each tablet also contains the following inactive ingredients: Croscarmellose sodium, hypromellose, iron oxide yellow, magnesium stearate, maltodextrin, medium chain triglycerides, microcrystalline cellulose, polydextrose, povidone, talc, titanium dioxide.

Nature and contents of the container:
Cartons of 60 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

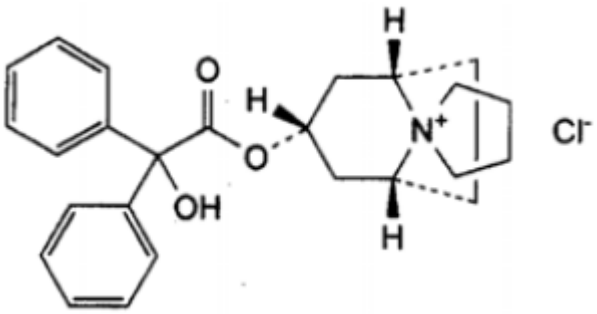
Proper name: Trospium chloride

Chemical name: (1R,3r,5S)-3-[(Hydroxydiphenylacetyl)oxy]spiro[8-azoniabicyclo[3.2.1] octane 8,1-'pyrrolidinium] chloride

Molecular formula and molecular mass:

Molecular formula: $C_{25}H_{30}ClNO_3$ Molecular mass: 427.97 g/mol

Structural formula:



Physicochemical properties: Trospium chloride is a white to almost white crystalline powder

The compound's solubility in water is approximately 1 g/2 mL.

n-Octanol/phosphate buffer (pH 7.4) = 0.038. The molecule is hydrophilic and highly charged.[4]

CLINICAL TRIALS

Comparative Bioavailability

A randomized, four-period, fully replicated, two-treatment, two-sequence, single oral dose, crossover bioequivalence study comparing Accel-Trospium to Regurin (trospium), Madaus GrnbH, (Germany), was conducted in healthy, adult male subjects under fasting conditions. Fifty seven subjects were included in the statistical analysis; the results are summarized below:

SUMMARY TABLE OF THE COMPARATIVE BIO AVAILABILITY DATA

TROSPIUM (1 x 20 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (pg·hrs/mL)	42108.02 50979.24 (65.8)	44505.09 52123.90 (57.0)	95.8	88.6 - 103.6
AUC_I (pg·hrs/mL)	43720.05 52878.43 (63.3)	46175.56 53701.34 (55.9)	95.7	88.9 - 103.1
C_{max} (pg/mL)	3363.28 4156.46 (71.9)	3575.62 4284.06 (63.8)	94.5	86.3 - 103.6
T_{max}§ (h)	4.67 (2.50 - 11.00)	4.67 (2.50 - 8.00)		
$T_{1/2}$ᶜ (h)	18.51 (19.9)	18.18 (22.2)		

* Accel-Trospium
† Regurin, Madaus GmbH, (Germany), purchased in the UK
§ Expressed as the median (range) only
ᶜ Expressed as the arithmetic mean (CV%) only

Study demographics and trial design

Trospium chloride was evaluated for the treatment of patients with overactive bladder who had symptoms of urinary frequency, urgency, and urge incontinence in two US 12-week, placebo-controlled studies and one 9-month open label extension[1, 2].

Study 1[1] was a randomized, double-blind, placebo-controlled, parallel-group study in 523 patients. A total of 262 patients received trospium chloride 20 mg twice daily and 261 patients received placebo. The majority of patients were Caucasian (85%) and female (74%) with a mean age of 61 years (range 21 to 90 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge), urge incontinence episodes of at least 7 per week, and greater than 70 micturitions per week. The patient=s medical history and urinary diary during the treatment-free

baseline confirmed the diagnosis.

Study 2[2] was nearly identical in design to Study 1. A total of 329 patients received trospium chloride 20 mg twice daily and 329 patient received placebo. The majority of patients were Caucasian (88%) and female (82%) with a mean age of 61 years (range 19 to 94 years). Entry criteria were identical to Study 1.

Table 3 - Summary of patient demographics: Studies 1 and 2

	Trial design	Dosage (route) and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 1	Randomized, double-blind, placebo-controlled, parallel-group plus open-label treatment phase	Trospium chloride 20 mg bid (oral) Placebo bid (oral) 12-week double-blind treatment phase plus 9-month open-label treatment phase	Trospium chloride: N = 262 Placebo: N = 261	61 yrs (21-90 yrs)	134M/389F
Study 2	Randomized, double-blind, placebo-controlled, parallel-group	Trospium chloride 20 mg bid (oral) Placebo bid (oral) 12-week double-blind treatment phase	Trospium chloride: N = 329 Placebo: N = 329	61 yrs (19-94 yrs)	122M/536F

M = male, F = female, yrs = years

Study results

Study 1: Reductions in urinary frequency, urge incontinence episodes and urinary void volume for placebo and trospium chloride treatment groups are summarized in **Table 4** and **Figure 2** and ***Figure 3***.

Table 4 - Mean (SE) change from baseline to end of treatment (Week 12 or last observation carried forward) for urinary frequency, urge incontinence episodes, and void volume in Study 1

Efficacy endpoint	Placebo N=256	Trospium chloride N=253	P-value
Urinary frequency/24 hours [a,*]			
Mean baseline	12.9	12.7	<0.001
Mean change from baseline	-1.3 (0.2)	-2.4 (0.2)	
Urge incontinence episodes/week [b,*]			
Mean baseline	30.1	27.3	0.012
Mean change from baseline	-13.9 (1.2)	-15.4 (1.1)	
Urinary void volume/toilet void (mL) [a, c]			
Mean baseline	156.6	155.1	<0.001
Mean change from baseline	7.7 (3.1)	32.1 (3.1)	

[a] Treatment differences assessed by analysis of variance for ITT:LOCF data set.
[b] Treatment differences assessed by ranked analysis of variance for ITT:LOCF data set.
[c] Placebo N=253, trospium chloride N=248.
[*] Denotes co-primary endpoint.
ITT=intent-to-treat, LOCF=last observation carried forward.

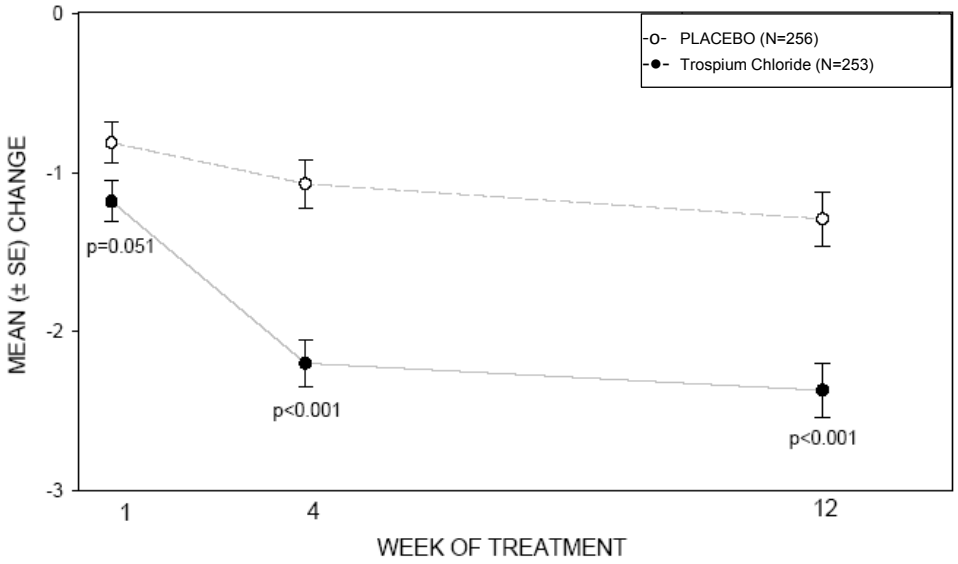


Figure 2 - Mean Change from Baseline in Urinary Frequency/24 Hours, by Visit: Study 1

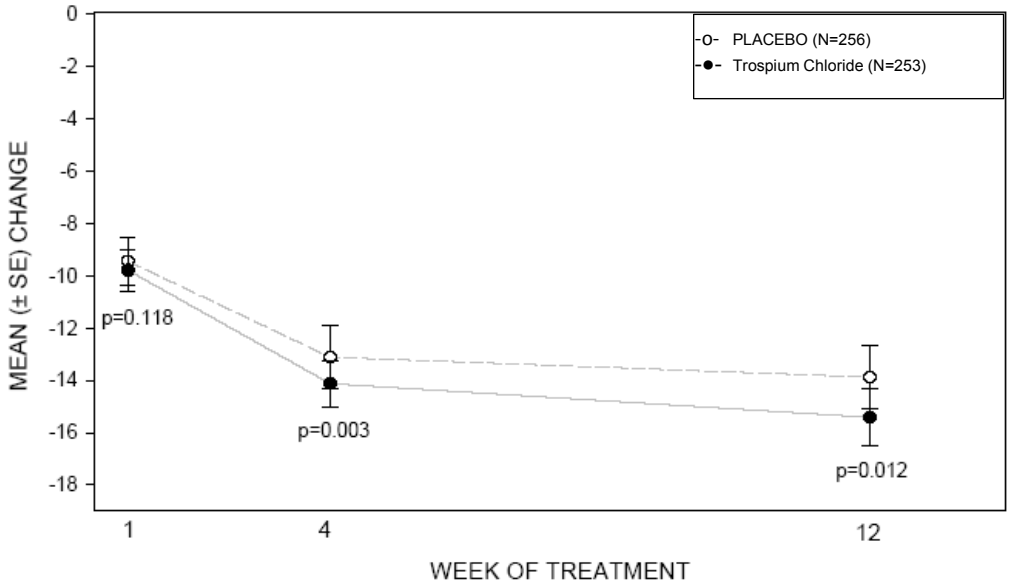


Figure 3 - Mean Change from Baseline in Urge Incontinence/Week, by Visit: Study 1

Study 2: Reductions in urinary frequency, urge incontinence episodes, and urinary void volume for placebo and trospium chloride treatment groups are summarized in **Table 5** and **Figure 4** and **Figure 5**.

Table 5 - Mean (SE) change from baseline to end of treatment (Week 12 or last observation carried forward) for urinary frequency, urge incontinence episodes, and void volume in Study 2

Efficacy endpoint	Placebo N=325	Trospium chloride N=323	P-value
Urinary frequency/24 hours [a,*]			
Mean baseline	13.2	12.9	<0.001
Mean change from baseline	-1.8 (0.2)	-2.7 (0.2)	
Urge incontinence episodes/week [b]			
Mean baseline	27.3	26.9	<0.001
Mean change from baseline	-12.1 (1.0)	-16.1 (1.0)	
Urinary void volume/toilet void (mL) [a, c]			
Mean baseline	154.6	154.8	<0.001
Mean change from baseline	9.4 (2.8)	35.6 (2.8)	

[a] Treatment differences assessed by analysis of variance for ITT:LOCF data set.
[b] Treatment differences assessed by ranked analysis of variance for ITT:LOCF data set.
[c] Placebo N=320, trospium chloride N=319.
[*] Denotes co-primary endpoint.
ITT=intent-to-treat, LOCF=last observation carried forward.

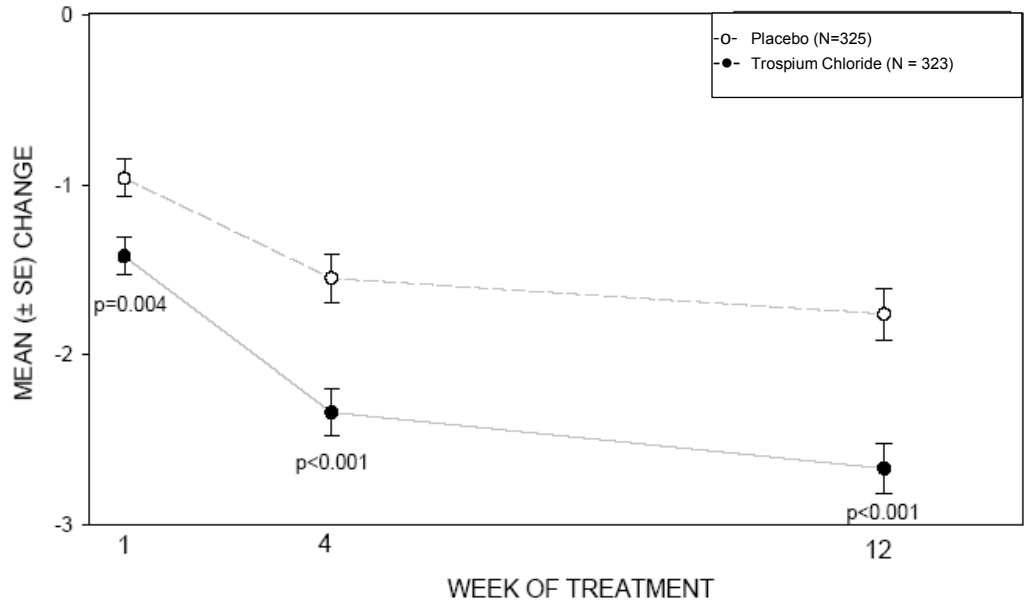


Figure 4 - Mean Change from Baseline in Urinary Frequency/24 Hours, by Visit: Study 2

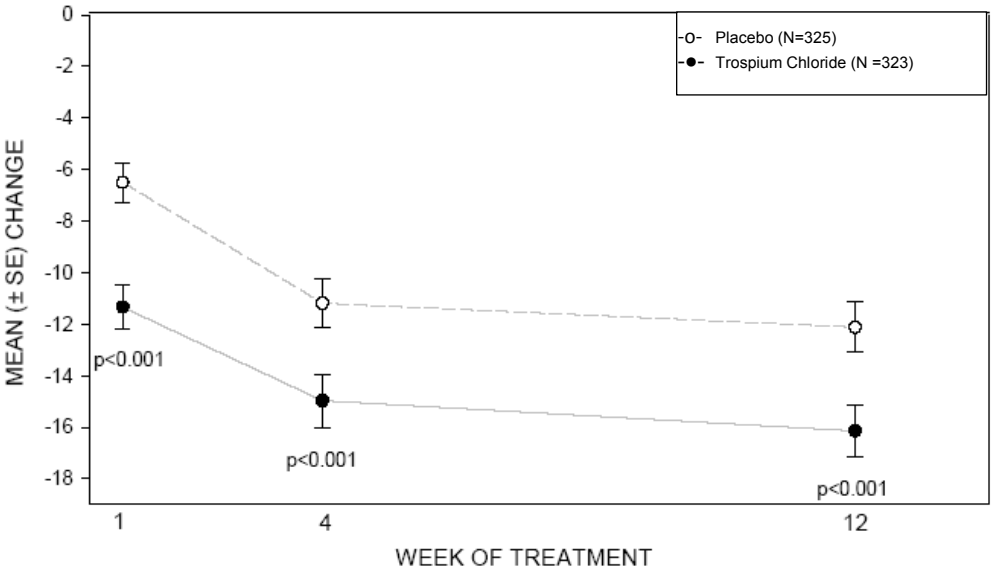


Figure 5 - Mean Change from Baseline in Urge Incontinence/Week, by Visit: Study 2

In addition to the placebo-controlled studies, active-controlled, randomized, double-blind, multi-centre trials, ranging from 2 to 52 weeks in duration, compared trospium chloride to oxybutynin hydrochloride, in patients with detrusor instability or detrusor hyperreflexia. Trospium chloride had comparable efficacy to oxybutynin, but better tolerability[5, 6].

DETAILED PHARMACOLOGY

ANIMAL

Pharmacodynamics

Intravenous administration of trospium chloride to female rats produced marked inhibition of cholinergic spasms when acetylcholine was dripped onto the exteriorised bladder. Effects of trospium chloride have also been demonstrated on lower urinary tract functions in the dog.

Trospium chloride demonstrates high affinity for muscarinic receptors, with equipotent binding to M_2 and M_3 receptors (pKi values: 9.2 and 9.3)[4].

Pharmacokinetics

Placental transfer and distribution in milk

Gestating rats were given 50 μg/kg ^{3}H-trospium chloride by i.v. injection on the 10th, 16th and 20th day of gestation. Only small amounts of the hydrophilic trospium chloride crossed into the placenta. Trospium chloride concentrations in the placenta were similar to those in blood but lower than in the liver, kidneys and heart. The highest radioactivity concentrations in the fetal organs occurred in the livers.

The transfer of ^{3}H-trospium chloride and its metabolites into the milk of lactating rats after oral and i.v. administration was determined between the 7th and 9th day postpartum. The percentage of i.v. injected trospium chloride activity excreted into the milk within 24 hours was 4.36×10^{-2}. Generally, trospium chloride and azoniaspironortropanol (as the only metabolite) were present. After oral administration, the milk levels never exceeded the blood levels.

HUMAN

Pharmacokinetics

Absorption and bioavailability

Linear dependence of dose was established for PK parameters. Mean absolute bioavailabilities for oral doses of 20, 40, and 60 mg were 9.6%, 10.8%, and 12%, respectively, with an overall absolute bioavailability of 10.8%. Mean absorption rates for oral doses of 20, 40, and 60 mg were 14.6%, 13.2%, and 14.3%, respectively, with an overall absorption rate of 14% of dose. C_{max} occurred approximately 5 hours post-dose, showing slow drug absorption.

Following 20 mg bid dosing for 6 days, trospium chloride plasma concentrations at steady-state on Day 6 were 1.56 ng/mL vs. 1.2 ng/mL following a single dose of 20 mg.

AUC and C_{max} values were 70-80% lower under fed versus fasted conditions. 90% CIs for the PK parameters of AUC_{0-4} and C_{max} fell outside the CI limits of acceptance. The CI for half value duration (HVD) slightly overlapped the CI limits of acceptance. Thus, the absorption of trospium chloride from the GI tract may be altered by concomitant food intake. Due to the food effects observed, it is recommended that trospium chloride be taken on an empty stomach (see "**DOSAGE AND ADMINISTRATION**").

C_{max} and AUC values decreased up to 59% and 33%, respectively, when trospium chloride was administered in the evening compared to in the morning. (See "**ACTION AND CLINICAL PHARMACOLOGY**").

Distribution and protein binding

In plasma protein binding studies with human serum, binding rates between the range of approximately 48 to 78% over various concentration ranges were observed. These rates do not suggest any likely interference with other drugs. Competitive plasma protein binding is also unlikely due to low plasma concentration exposure at the therapeutic dose (<10 ng/mL after a single 40 mg dose)**.**

The plasma to whole blood ratio of non-volatile ^{3}H-trospium chloride was 1:6:1 at 0.75 hours post-dose (single i.v. target dose of 1 mg in healthy male subjects). Given that the normal hematocrit is approximately 45% in healthy men, the 1:6:1 ratio translates to a 12% distribution of ^{3}H-trospium chloride in blood cells.

Metabolism and excretion

Trospium chloride has negligible inhibitory effects on seven cytochrome P450 isoenzymes, including CYP3A4 and CYPD26 based on *in vitro* data[3].

After oral administration, 60% of the radioactivity excreted in urine was unchanged trospium, demonstrating first pass metabolism. The mean renal clearance rate observed (29.07 L/hour) indicates that trospium is actively secreted into the urine.

Following intravenously administered radio-labelled trospium chloride, more than 90% of the dose was recovered; approximately 70% in urine and 20% in faeces. Greater than 80% of the radioactivity excreted in urine was [^{3}H]-trospium. The major metabolite, azoniaspironortropanol, represented approximately 10% of the excreted dose in urine. In addition, 2 unknown metabolites combined to represent less than 10% of the excreted dose.

TOXICOLOGY

Single-Dose Toxicity:

In mice and rats, oral and i.v. dosing of trospium chloride produced similar effects:

The calculated LD_{50} for mice is 425 mg/kg oral and 7.5 mg/kg i.v. for males and 365 mg/kg oral and 8.4 mg/kg i.v. for females.

In rats, high oral doses (630 - 1260 mg/kg) produced clinical signs of hyperactivity, tremor, spasms, and tonoclonic convulsions after 10 minutes. After 1 hour, reduced activity was observed. During the first 24 hours of dosing, impaired coordination (males), postural abnormalities, diminished elicitation of reflexes (females), reduction in grip strength and tone of the extremities (females), changes in the colour of the skin and mucous membranes, piloerection (males) and lowered body temperature were observed. Death occurred within 24 hours after dosing. The LD_{50} calculated for rats is 940 mg/kg for males and 800 mg/kg for females [the maximum recommended daily dosing for humans is 40 mg (20 mg bid)]. Similar reactions were observed after i.v. administration, with additional effects of cyanosis and bradypnoea. The animals died within 5 minutes after injection. The calculated LD_{50} is 10.7 mg/kg for males and
12.3 mg/kg for females.

Repeat-Dose Toxicity:

In rats dosed orally with 200 mg/kg trospium chloride for approximately 35 weeks, body weight gain was observed.

In dogs, food consumption and body weight gain were slightly lower after receiving 60 mg/kg for 26 weeks. Mydriasis with photophobia, impaired pupillary accommodation, corneal lesions as well as raised mucus production were also observed. One male died of bacterial bronchopneumonia, possibly due to a treatment-related increase of mucus secretion.

Genotoxicity:

Trospium chloride was not genotoxic in a number of *in-vitro* assays such as the Ames test, mouse lymphoma test and mitotic gene conversion and chinese hamster ovary assays.

In an in-vivo micronucleus test in rats, trospium chloride did not induce significant levels of micronucleated polychromatic erythrocytes in bone marrow cells following administration of a single oral dose of 400 mg/kg.

Carcinogenicity:

In a 78 week study in mice, body weight gain and intestinal distension similar to that seen in rats, described below, were observed. Increased lung adenomas in males (20 mg/kg) and females

(2 mg/kg) were observed. The incidences of proliferative lung lesions were most likely due to chance and not an effect of trospium chloride.

In a 24-month rat study, there was a distinct reduction in body weight gain at a 200 mg/kg doses in males and females and in females only at 20 mg/kg. Bowel distension was observed in all treated groups. Trospium chloride did not increase the overall tumor incidence, and no tumor types were found that are uncommon in the rat strain used.

Reproductive and Developmental Toxicity:

Reproductive function

In the rat, trospium chloride caused no impairment of male and female fertility in treated parents (F_o) or their untreated offspring. Furthermore, the breeding and rearing behaviour and the postnatal development were entirely normal throughout.

Trospium chloride was well tolerated by dams of trospium chloride treated rats and examination of the fetuses revealed no embryotoxic or teratogenic effects.

A test on rabbits showed no compound-specific effects in either dams or fetuses.

In female rats given trospium chloride from the 15th day of gestation until the end of the lactation period, dose-related effects occurring at doses of 2, 20 and 200 mg/kg consisted of rapid and irregular breathing, pupillary dilatation and increased excitability. Towards the end of the lactation period, two females died within one hour of dosing (200 mg/kg). Rearing performance of the dams was normal, and only the females given 200 mg/kg gained slightly less body weight in the gestation period than the controls. The postnatal development of the offspring was invariably normal.

Local Tolerance:

Good local (gastro-intestinal) tolerance has been shown in various long-term studies.

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PART III: CONSUMER INFORMATION

PrACCEL-TROSPIUM
Trospium Chloride Tablets

This leaflet is part III of a three-part "Product Monograph" published when ACCEL-TROSPIUM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ACCEL-TROSPIUM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ACCEL-TROSPIUM is an antispasmodic agent used to treat overactive bladder. Patients with overactive bladder have these symptoms: a strong need to urinate right away (urgency) with or without urge incontinence (leaking or wetting accidents caused by a sudden, unstoppable urge to urinate), usually with a need to urinate often (frequent bathroom visits), and nocturia (having to urinate frequently during the night).

What it does:
The term "overactive bladder" refers to the involuntary spasm of the bladder muscle (detrusor). Overactive bladder happens when you cannot control your bladder muscle contractions. When these muscle contractions happen too often or cannot be controlled, you get symptoms of overactive bladder (see "What the medication is used for:").

ACCEL-TROSPIUM blocks involuntary contractions of the bladder muscle (detrusor) which allows the muscle to relax giving you better control of your bladder.

ACCEL-TROSPIUM reduces (see also "What this medication is used for"):

- the strong need to urinate right away
- the number of bathroom visits during the day or night
- the number of wetting accidents

You should begin to notice an improvement in your symptoms in about a week.

When it should not be used:
ACCEL-TROSPIUM should not be used by patients with or at risk for:

- an inability to empty the bladder (urinary retention);
- delayed emptying of the stomach (gastric retention);
- an eye problem called "uncontrolled narrow-angle glaucoma";
- a history of any allergic or other severe reaction to ACCEL-TROSPIUM or any of its components.

What the medicinal ingredient is:
Trospium chloride

What the nonmedicinal ingredients are:
Croscarmellose sodium, hypromellose, iron oxide yellow, magnesium stearate, maltodextrin, medium chain triglycerides, microcrystalline cellulose, polydextrose, povidone, talc, titanium dioxide.

What dosage forms it comes in:
ACCEL-TROSPIUM is available as a coated tablet (20 mg).

WARNINGS AND PRECAUTIONS

BEFORE you use ACCEL-TROSPIUM talk to your doctor or pharmacist if:

- you have trouble emptying your bladder (slow urinary stream), because of the risk of urinary retention;
- you have delayed or slow emptying of your stomach because of the risk of gastric retention;
- you have ulcerative colitis (ulcers in the large intestine or colon), intestinal atony or myasthenia gravis (muscle weakness);
- you have an eye problem called "narrow-angle glaucoma" that is being treated;
- you have liver or kidney disease (see "PROPER USE OF THIS MEDICATION", Usual dose);
- you have congestive heart failure, hypokalemia (low potassium), or other conditions which may increase the risk of ACCEL-TROSPIUM affecting your heart rate;
- you have heart disease
- you are pregnant, planning on becoming pregnant or are breast feeding;

The safety and effectiveness of ACCEL-TROSPIUM has not been studied in children.

Although uncommon, ACCEL-TROSPIUM may cause blurred vision and/or drowsiness in some people. Until you know how ACCEL-TROSPIUM affects you, caution should be exercised when driving or operating heavy machinery.

Consumption of alcohol while taking ACCEL-TROSPIUM may make drowsiness worse.

Due to decreased sweating, heat prostration (overheating of the body) can occur when drugs such as ACCEL-TROSPIUM are used in a hot environment.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ACCEL-TROSPIUM include: anticholinergic agents (such as amantadine, tricyclic antidepressants, quinidine, antihistamines, and disopyramide), beta agonists (such as salbutamol or formoterol), prokinetic agents (such as metoclopramide) and drugs that are eliminated by active renal secretion (such as digoxin, procainamide, pancuronium, morphine, vancomycin, metformin and tenofovir).

Tell your doctor or pharmacist about every medication you are taking including those you are taking without a prescription as well as any natural health products (herbal or vitamins).

Interactions with herbal medicines have not been studied.

Taking ACCEL-TROSPIUM with food reduces the amount of medication that will get into your body. (see "PROPER USE OF THIS MEDICATION")

PROPER USE OF THIS MEDICATION

Usual dose:
Take one ACCEL-TROSPIUM 20 mg tablet twice a day on an empty stomach at least one hour before meals. For patients with kidney disease the recommended dose of ACCEL-TROSPIUM is 20 mg once a day. In geriatric patients 75 years of age and older, the dose may be reduced to 20 mg once daily if twice daily dosing is not well tolerated.

ACCEL-TROSPIUM has not been studied in children.

Overdose:
Overdosage with ACCEL-TROSPIUM may result in severe anticholinergic effects such as rapid and irregular heartbeat, flushed face, fever, ringing in the ears, and muscle spasms.

If you think you have taken an overdose of ACCEL-TROSPIUM, go to your nearest emergency room immediately. If possible, bring the package with you.

Missed Dose:
If you miss a dose, take your next dose at the usual time (on an empty stomach at least 1 hour before your next meal). Do not double the next dose to make up for the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects:
In clinical studies, the most common side effects with trospium chloride were dry mouth, constipation and abdominal pain.

Other side effects:
The following less common events may also occur with the use of trospium chloride: dyspepsia (upset stomach), nausea, dizziness, flatulence, chest pain, dry eyes, blurred vision, increased heart rate, palpitation, urinary retention, and heat prostration.

Due to decreased sweating, heat prostration (overheating of the body) can occur when drugs such as ACCEL-TROSPIUM are used in a hot environment. Be sure to consume adequate amounts of liquid if you are in a hot environment for a prolonged period of time.

Tell your doctor or pharmacist if you have any side effects that bother you or don't go away.

The following events have rarely been reported during trospium chloride use: Anaphylactic, Stevens-Johnson and toxic epidermal necrolysis reactions (rare, life-threatening, allergic reactions), angioedema (serious allergic reaction which can cause swelling of the face or throat), tachycardia (rapid heartbeat), syncope (fainting), myalgia (muscle pain), arthralgia (joint pain), rhabdomyolysis (destruction of muscle tissue), hallucinations, confusion, agitation, and hypertensive crisis (sudden, marked increase in blood pressure). If you think you are experiencing any of these rare effects, stop taking ACCEL-TROSPIUM immediately and go to the emergency room.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Urinary retention (inability to empty your bladder)			√
	Constipation	√		

This is not a complete list of side effects. For any unexpected effects while taking ACCEL-TROSPIUM, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature 15° to 30°C.

Keep out of reach and sight of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about ACCEL-TROSPIUM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting https://www.canada.ca/en/health-canada.html; the manufacturer's website www.accelpharma.com, or by calling 1-877-822-2235.

This leaflet was prepared by Accel Pharma Inc.

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