

PRODUCT MONOGRAPH

Pr **TROSEC**[®]

Tropium Chloride

Coated Tablet 20 mg

ATC G04BD09

Antispasmodic

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Trospium Chloride

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	coated tablet/20 mg	lactose monohydrate <i>For a complete listing of all nonmedicinal ingredients see "Dosage Forms, Composition and Packaging".</i>

INDICATIONS AND CLINICAL USE

TROSEC[®] (trospium chloride) is indicated for:

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

CONTRAINDICATIONS

TROSEC 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 TROSEC, 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 TROSEC are used in a hot environment. Because anticholinergics such as TROSEC 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

TROSEC should be administered with caution to patients with gastrointestinal obstructive

disorders because of the risk of gastric retention (see “CONTRAINDICATIONS”). TROSEC, 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, TROSEC 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 TROSEC 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 TROSEC was chosen because this dose achieves the C_{max} expected in severe renal impairment. TROSEC 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 TROSEC 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 TROSEC-treated overactive bladder patients (See “CLINICAL TRIALS”). The clinical significance of T wave inversion in this study is unknown.

TROSEC is associated with an increase in heart rate that correlates with increasing plasma concentrations. In the study described above, TROSEC 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.

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

Hepatic/Biliary/Pancreatic

Caution should be used when administering TROSEC 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.

Renal

TROSEC 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 [Cl_{cr} 0.25 - 0.5 mL/sec (15 - 30 mL/min)]. In such patients, TROSEC should be administered as 20 mg once a day at bedtime (see "DOSAGE AND ADMINISTRATION"). The use of TROSEC 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 TROSEC 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. TROSEC 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 TROSEC is administered to a nursing woman. TROSEC should be used during lactation only if the potential benefit justifies the potential risk to the newborn.

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

Geriatrics (≥ 75 years of age): Of the 262 patients with overactive bladder who received treatment with TROSEC in the US 12-week clinical study, 120 patients (45.8%) were 65 years of age and older. Forty-two TROSEC-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 TROSEC (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 TROSEC 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 ng·h/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 ng·h/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 TROSEC was evaluated in Phase 2 and 3 controlled clinical trials in a total of 2975 patients, who were treated with TROSEC (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 TROSEC 20 mg twice daily. In all controlled trials combined, 232 and 208 patients received treatment with TROSEC 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 TROSEC 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 TROSEC 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 TROSEC by the investigator, were reported by at least 1% of patients, and were reported more frequently in the TROSEC group than in the placebo group.

The two most common adverse events reported by patients receiving TROSEC 20 mg bid were dry mouth and constipation. The single most frequently reported adverse event for TROSEC, dry mouth, occurred in 20.1% of TROSEC 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 TROSEC 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 TROSEC, reported in $\geq 1\%$ of all patients treated with TROSEC and more frequent with TROSEC (20 mg bid) than placebo in Studies 1¹ and 2² combined

Adverse Event	Placebo (N=590)	TROSEC 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 TROSEC by the investigator, occurring in $\geq 0.5\%$ of TROSEC-treated patients, and more common with TROSEC 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, anaphylactic reaction, syncope, rhabdomyolysis, vision abnormal, hallucinations and delirium, and "hypertensive crisis".

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 TROSEC 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 TROSEC or to assess the effect of TROSEC on the pharmacokinetics of other drugs. TROSEC 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 TROSEC with drugs that are eliminated by active renal tubular secretion may increase the serum concentration of TROSEC 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 TROSEC with food has been shown to reduce drug absorption (See "ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Effect of Food"). TROSEC 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 TROSEC 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 \geq 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 TROSEC in patients with renal function <0.25 mL/sec (15 mL/min) has not been studied.

In geriatric patients \geq 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 TROSEC 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

TROSEC should be dosed at least one hour before meals or given on an empty stomach.

OVERDOSAGE

Overdosage with TROSEC 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TROSEC 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 TROSEC increases maximum cystometric bladder capacity and volume at first detrusor contraction.

Pharmacokinetics

A summary of mean (\pm standard deviation) pharmacokinetic parameters for a single 20 mg dose of TROSEC is provided in Table 2.

Table 2 - Mean (\pm SD) Pharmacokinetic Parameter Estimates for a Single 20 mg TROSEC Dose in Healthy Volunteers

C_{\max} (ng/mL)	$AUC_{0-\infty}$ (ng/mL·hr)	T_{\max} (hr)	$t_{1/2}$ (hr)
3.5 ± 4.0	36.4 ± 21.8	5.3 ± 1.2	18.3 ± 3.2

The mean plasma concentration-time (\pm SD) profile for TROSEC is shown in Figure 1.

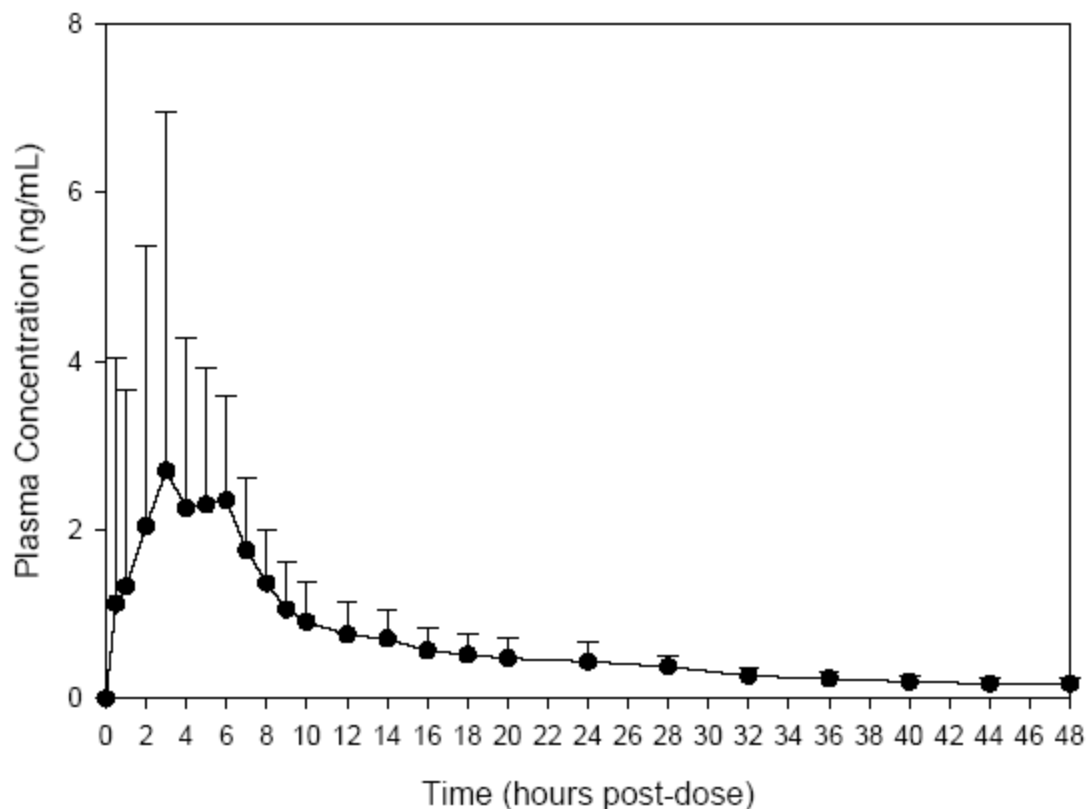


Figure 1 - Mean (+ SD) Concentration-Time Profile for a Single 20 mg Oral Dose of TROSEC in Healthy Volunteers

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. TROSEC 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 TROSEC was administered while fasting. Therefore, it is recommended that TROSEC 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 ³H-trospium chloride ratio of plasma to whole blood was 1.6:1. This ratio indicates that the majority of ³H-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 chloride³.

Excretion: The plasma half-life for TROSEC following oral administration is approximately 20 hours. After administration of oral ¹⁴C-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 TROSEC were not evaluated in pediatric patients.

Geriatrics: Age did not appear to significantly affect the pharmacokinetics of TROSEC 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 TROSEC dose was administered to 16 elderly subjects, exposure was 45% lower in elderly females compared to elderly males. When 20 mg TROSEC 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 TROSEC. 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 TROSEC 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 TROSEC. A 4.5-fold and 2-fold increase in mean $AUC_{0-\infty}$ 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 TROSEC in patients with severe renal insufficiency necessitates adjustment of dosage frequency. The pharmacokinetics of TROSEC 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 TROSEC 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 of children.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Pharmaceutical form:

Brownish yellow, biconvex, glossy coated tablets, imprinted with a ‘T’.

Composition:

Each tablet contains 20 mg of trespium chloride.

Each tablet also contains the following inactive ingredients: sucrose, wheat starch, microcrystalline cellulose, talc, lactose monohydrate, calcium carbonate, titanium dioxide, stearic acid, croscarmellose sodium, povidone, polyethylene glycol 8000, colloidal silicon dioxide, ferric oxide, carboxymethylcellulose sodium, white wax, carnauba wax.

Nature and contents of the container:

Blister packs of 10.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Trospium chloride

Chemical name:

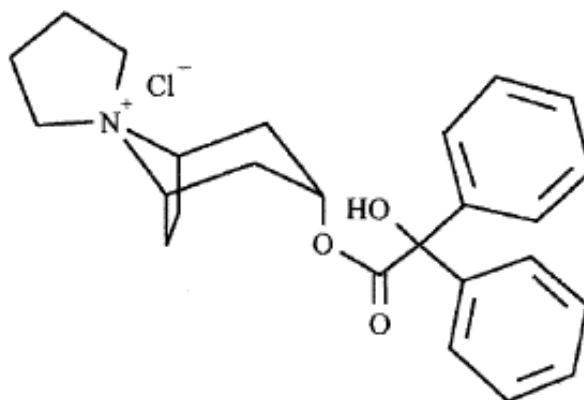
Spiro[8-azoniabicyclo[3,2,1]octane-8,1'-pyrrolidinium]-3-[(hydroxydiphenyl-acetyl)-oxy]-chloride(1 α , 3 β , 5 α)-(9Cl)

Molecular formula and molecular mass:

Molecular formula: C₂₅H₃₀ClNO₃

Molecular mass: 427.97

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

Study demographics and trial design

TROSEC 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 1¹ was a randomized, double-blind, placebo-controlled, parallel-group study in 523 patients. A total of 262 patients received TROSEC 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 2² was nearly identical in design to Study 1. A total of 329 patients received TROSEC 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	TROSEC 20 mg bid (oral) Placebo bid (oral) 12-week double-blind treatment phase plus 9-month open-label treatment phase	TROSEC: N = 262 Placebo: N = 261	61 yrs (21-90 yrs)	134M/389F
Study 2	Randomized, double-blind, placebo-controlled, parallel-group	TROSEC 20 mg bid (oral) Placebo bid (oral) 12-week double-blind treatment phase	TROSEC: 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 TROSEC treatment groups are summarized in Table 4 and Figures 2 and 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	TROSEC N=253	P-value
Urinary frequency/24 hours^{a,*}			
Mean baseline	12.9	12.7	
Mean change from baseline	-1.3 (0.2)	-2.4 (0.2)	<0.001
Urge incontinence episodes/week^{b,*}			
Mean baseline	30.1	27.3	
Mean change from baseline	-13.9 (1.2)	-15.4 (1.1)	0.012
Urinary void volume/toilet void (mL)^{a,c}			
Mean baseline	156.6	155.1	
Mean change from baseline	7.7 (3.1)	32.1 (3.1)	<0.001
^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, TROSEC N=248. * Denotes co-primary endpoint. ITT=intent-to-treat, LOCF=last observation carried forward.			

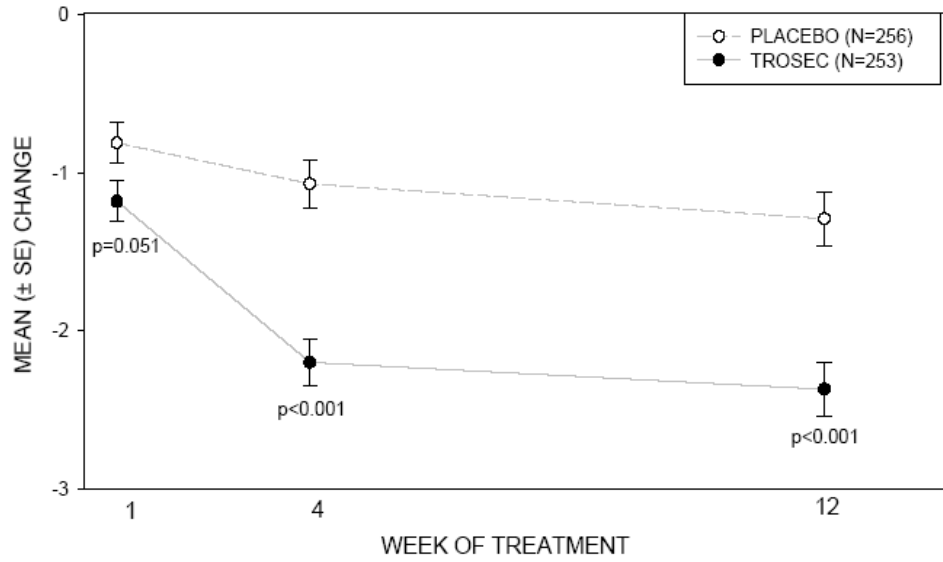


Figure 2 - Mean Change from Baseline in Urinary Frequency/24 Hours, by Visit: Study 1

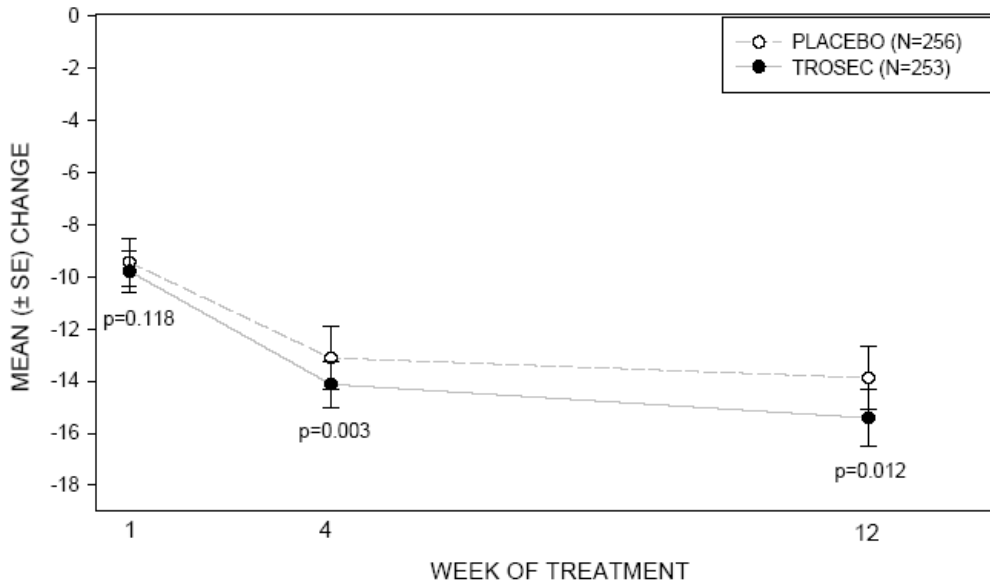


Figure 3 - Mean Change from Baseline in Urge Incontinence/Week, by Visit: Study 1

Study 2: Reductions in urinary frequency, urge incontinence episodes, and urinary void volume for placebo and TROSEC treatment groups are summarized in Table 5 and Figures 4 and 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	TROSEC N=323	P-value
Urinary frequency/24 hours^{a,*}			
Mean baseline	13.2	12.9	
Mean change from baseline	-1.8 (0.2)	-2.7 (0.2)	<0.001
Urge incontinence episodes/week^b			
Mean baseline	27.3	26.9	
Mean change from baseline	-12.1 (1.0)	-16.1 (1.0)	<0.001
Urinary void volume/toilet void (mL)^{a,c}			
Mean baseline	154.6	154.8	
Mean change from baseline	9.4 (2.8)	35.6 (2.8)	<0.001
^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, TROSEC N=319. * Denotes co-primary endpoint. ITT=intent-to-treat, LOCF=last observation carried forward.			

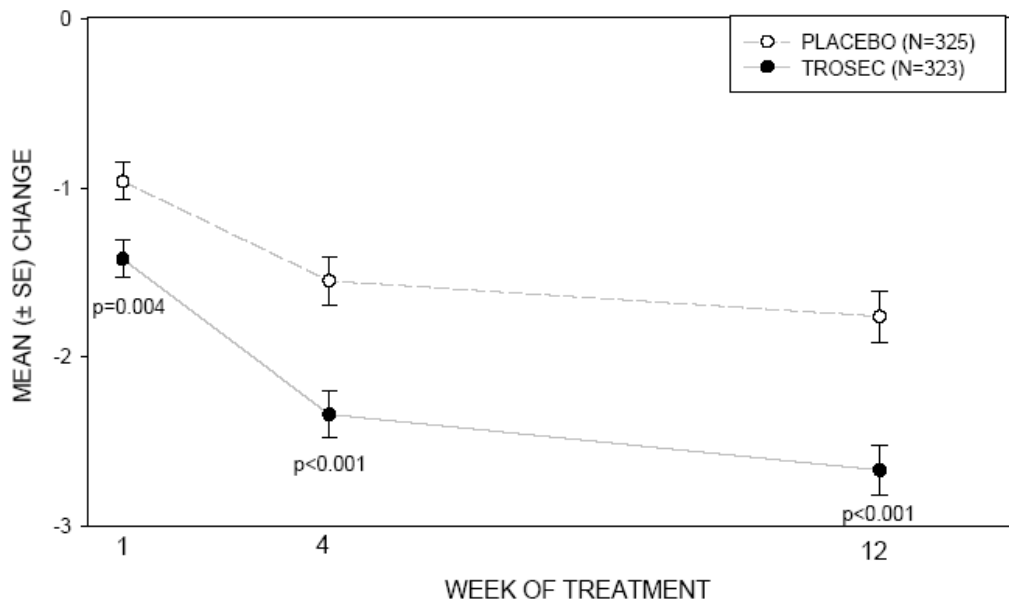


Figure 4 - Mean Change from Baseline in Urinary Frequency/24 Hours, by Visit: Study 2

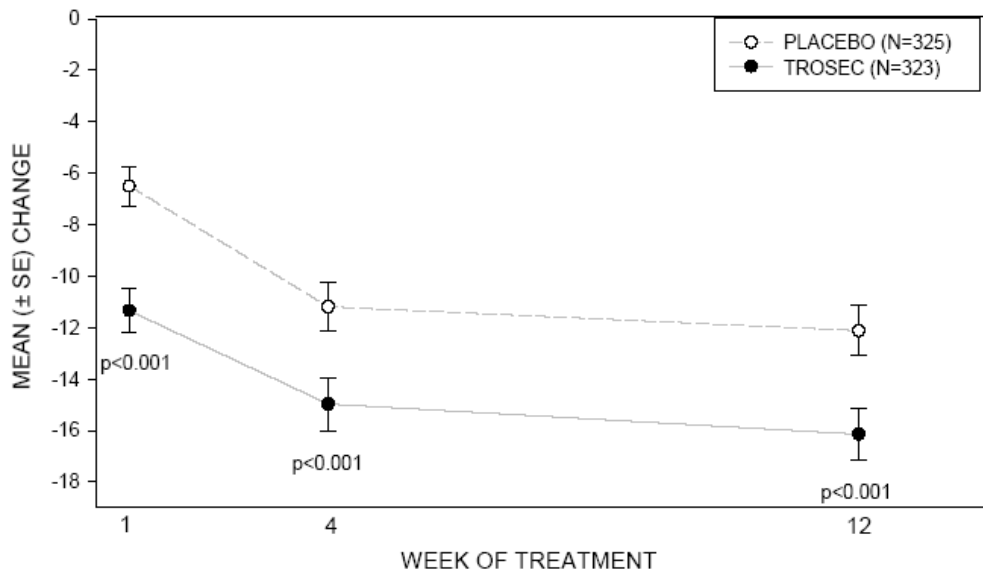


Figure 5 - Mean Change from Baseline in Urge Incontinence/Week, by Visit: Study 2

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 M₂ and M₃ receptors (pK_i values: 9.2 and 9.3)⁴.

Pharmacokinetics

Placental transfer and distribution in milk

Gestating rats were given 50 µg/kg ³H-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 ³H-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 x 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 $AUC_{0-\infty}$ 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 TROSEC be taken on an empty stomach (see "DOSAGE AND ADMINISTRATION").

C_{max} and AUC values decreased up to 59% and 33%, respectively, when TROSEC 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 ^3H -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 ^3H -trospium chloride in blood cells.

Metabolism and excretion

Trospium chloride has negligible inhibitory effects on seven cytochrome P450 isoenzymes, including CYP3A4 and CYP2D6 based on *in vitro* data³.

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 [^3H]-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 LD₅₀ 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 tonic-clonic 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 LD₅₀ 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 LD₅₀ 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 (F₀) 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**TROSEC®
Trospium Chloride**

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

ABOUT THIS MEDICATION**What the medication is used for:**

TROSEC 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:").

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

TROSEC 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:

TROSEC 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 TROSEC or any of its components.

What the medicinal ingredient is:

Trospium chloride

What the nonmedicinal ingredients are:

calcium carbonate, carboxymethylcellulose sodium, carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol 8000, povidone, stearic acid, sucrose, talc, titanium dioxide, wheat starch, white wax.

What dosage forms it comes in:

TROSEC is available as a coated tablet (20 mg).

WARNINGS AND PRECAUTIONS

BEFORE you use TROSEC 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 TROSEC affecting your heart rate;
- you are pregnant, planning on becoming pregnant or are breast feeding;

The safety and effectiveness of TROSEC has not been studied in children.

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

Consumption of alcohol while taking TROSEC may make drowsiness worse.

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

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with TROSEC 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 TROSEC with food reduces the amount of medication that will get into your body. (see "PROPER USE OF THIS MEDICATION")

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 TROSEC use: Anaphylactic and Stevens-Johnson reactions (rare, life-threatening, allergic reactions), tachycardia (rapid heartbeat), syncope (fainting), rhabdomyolysis (destruction of muscle tissue), and hypertensive crisis (sudden, marked increase in blood pressure). If you think you are experiencing any of these rare effects, stop taking TROSEC immediately and go to the emergency room.

PROPER USE OF THIS MEDICATION

Usual dose:

Take one TROSEC 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 TROSEC 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.

TROSEC has not been studied in children.

Overdose:

Overdosage with TROSEC 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 TROSEC, 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 TROSEC were dry mouth, constipation and abdominal pain.

Other side effects:

The following less common events may also occur with the use of TROSEC: 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 TROSEC are used in a hot

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 TROSEC, contact your doctor or pharmacist.

HOW TO STORE IT

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

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program
(CADRMP)
Health Canada
Address Locator: 0201C2
Ottawa, ON K1A 1B9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.sepracorpharma.ca>

or by contacting the sponsor, Sepracor Pharmaceuticals, Inc., at:
1-866-260-6291

This leaflet was prepared by Sepracor Pharmaceuticals, Inc.

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