HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SANCTURA XR® safely and effectively. See full prescribing information for SANCTURA XR®.

SANCTURA XR® (trospium chloride extended release capsules)
Initial U.S. Approval: 2004

INDICATIONS AND USAGE

SANCTURA XR® is a muscarinic antagonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage of SANCTURA XR® is one 60 mg capsule daily in the morning. SANCTURA XR® should be dosed with water on an empty stomach, at least one hour before a meal. (2)
- SANCTURA XR® is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/minute). (2)

DOSAGE FORMS AND STRENGTHS

- 60 mg capsules (3)

CONTRAINDICATIONS

SANCTURA XR® is contraindicated in

- patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and in patients who are at risk for these conditions (4)
- patients with known hypersensitivy (4)

WARNINGS AND PRECAUTIONS

- SANCTURA XR® should be administered with caution to patients with clinically significant bladder outflow obstruction or gastrointestinal obstructive disorders due to risk of urinary or gastric retention. (5.1, 5.3)
- Angioedema of the face, lips, tongue and/or larynx has been reported with trospium chloride. (5.2)
- In patients with narrow angle glaucoma, SANCTURA XR® should be used only with careful monitoring. (5.4)
- Central Nervous System Effects: Somnolence has been reported with SANCTURA XR®. Advise patients not to drive or operate heavy machinery until they know how SANCTURA XR® affects them. (5.5)
- SANCTURA XR® is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/minute). (5.6)
- Alcohol should not be consumed within 2 hours of SANCTURA XR® administration. (5.7)

ADVERSE REACTIONS

The most common adverse reactions (greater than or equal to 1%) with SANCTURA XR® are dry mouth (10.7%) and constipation (8.5%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan, Inc. at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Some drugs which are actively secreted by the kidney may interact with SANCTURA XR® by competing for renal tubular secretion. (7)
- Concomitant use with digoxin did not affect the pharmacokinetics of either drug. (7.1)
- Exposure to trospium on average was comparable in the presence of and without antacid, however, some individuals demonstrated increases or decreases in trospium exposure in the presence of antacid. The clinical relevance of these findings is not known. (7.2)
- Concomitant use with metformin immediate release tablets reduced exposure and peak concentration of trospium. (7.3)

USE IN SPECIFIC POPULATIONS

- The safety and effectiveness of SANCTURA XR® in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SANCTURA XR® is a muscarinic antagonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of SANCTURA XR® is one 60 mg capsule daily in the morning. SANCTURA XR® capsules should be dosed with water on an empty stomach, at least one hour before a meal.

SANCTURA XR® is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) *[see Warnings and Precautions (5.6), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

SANCTURA XR® is supplied as 60 mg capsules (white opaque body and orange opaque cap, printed with SAN 60).

4 CONTRAINDICATIONS

SANCTURA XR® is contraindicated in patients with:

- urinary retention
- gastric retention
- uncontrolled narrow-angle glaucoma
- known hypersensitivity to the drug or its ingredients. Angioedema, rash and anaphylactic reaction have been reported.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Urinary Retention

SANCTURA XR® capsules should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention *[see Contraindications (4)]*.

5.2 Angioedema

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

5.3 Decreased Gastrointestinal Motility

SANCTURA XR® should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention *[see Contraindications (4)]*. SANCTURA XR®, like other antimuscarinic agents, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony and myasthenia gravis .

5.4 Controlled Narrow-angle Glaucoma

In patients being treated for narrow-angle glaucoma, SANCTURA XR® should only be used if the potential benefits outweigh the risks, and in that circumstance only with careful monitoring *[see Contraindications (4)]*.

5.5 Central Nervous System Effects

SANCTURA XR® and SANCTURA® are associated with anticholinergic central nervous system (CNS) effects *[see Adverse Reactions (6.2)]*. A variety of CNS anticholinergic effects have been reported, including dizziness, confusion, hallucinations and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how SANCTURA XR ® affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

5.6 Patients with Severe Renal Impairment

SANCTURA XR® is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) *[see Dosage and Administration (2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

5.7 Alcohol Interaction

Alcohol should not be consumed within 2 hours of SANCTURA XR® administration. In addition, patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to SANCTURA XR® capsules in 578 patients for 12 weeks in two Phase 3 double-blind, placebo controlled trials (n=1165). These studies included overactive bladder patients of ages 21 to 90 years, of which 86% were female and 85% were Caucasian. Patients received 60 mg daily doses of SANCTURA XR®. Patients in these studies were eligible to continue treatment with SANCTURA XR® 60 mg for up to one year. From both these controlled trials combined, 769 and 238 patients received treatment with SANCTURA XR® for at least 24 and 52 weeks, respectively.

There were 157 (27.2%) SANCTURA XR® patients and 98 (16.7%) placebo patients who experienced one or more double-blind treatment-emergent adverse events (TEAEs) that were assessed by the investigator as at least possibly related to study medication. The most common TEAEs were dry mouth and constipation which, when reported, commonly occurred early in treatment (often within the first week). In the two Phase 3 studies, constipation, dry mouth, and urinary retention led to discontinuation in 1%, 0.7%, and 0.5% of patients treated with SANCTURA XR® 60 mg daily, respectively. In the placebo group, there were no discontinuations due to dry mouth or urinary retention and one due to constipation.

The incidence of serious adverse events was similar among patients receiving SANCTURA XR® and patients receiving placebo. No treatment-emergent serious adverse events in either treatment group were judged by the investigators as being possibly related to the study medication.

Table 1 lists those treatment emergent adverse events from the trials that were assessed by the investigator as possibly related to study medication, reported in at least 1% of SANCTURA XR® patients, and were more common for the SANCTURA XR® group than for placebo.

Table 1: Incidence of treatment-emergent adverse events reported in at least 1% of patients judged by the investigator as at least possibly related to treatment and more common for the SANCTURA XR® group than for placebo

	Number of patients (%)	
MedDRA Preferred term	**Placebo N=587**	**SANCTURA XR® N=578**
Dry mouth	22 (3.7)	62 (10.7)
Constipation	9 (1.5)	49 (8.5)
Dry eye	1 (0.2)	9 (1.6)
Flatulence	3 (0.5)	9 (1.6)
Nausea	2 (0.3)	8 (1.4)
Abdominal pain	2 (0.3)	8 (1.4)
Dyspepsia	4 (0.7)	7 (1.2)
Urinary tract infection	5 (0.9)	7 (1.2)
Constipation aggravated	3 (0.5)	7 (1.2)
Abdominal distension	2 (0.3)	6 (1.0)
Nasal dryness	0 (0.0)	6 (1.0)

Additional adverse events reported in less than 1% of SANCTURA XR® treated patients and more common for SANCTURA XR® than placebo, judged by the investigator at least possibly related to treatment were: vision blurred, feces hard, back pain, somnolence, urinary retention, and dry skin.

Table 2 lists all treatment-emergent adverse events for the trials reported in at least 2% of all SANCTURA XR® patients and more common for the SANCTURA XR® group than for placebo without regard to the investigator's judgment on drug relatedness.

Table 2: Incidence of treatment-emergent adverse events reported in at least 2% of patients regardless of reported relationship to treatment and more common for the SANCTURA XR® group than for placebo

	Number of patients (%)	
MedDRA Preferred term	**Placebo N=587**	**SANCTURA XR® N=578**
Dry mouth	22 (3.7)	64 (11.1)
Constipation	10 (1.7)	52 (9.0)
Urinary tract infection	29 (4.9)	42 (7.3)
Nasopharyngitis	10 (1.7)	17 (2.9)
Influenza	9 (1.5)	13 (2.2)

Additional adverse events reported in less than 2% of SANCTURA XR® treated patients and twice as frequent for SANCTURA XR® compared to placebo, regardless of reported relationship to treatment were: tachycardia, dry eyes, abdominal pain, dyspepsia, abdominal distension, constipation aggravated, nasal dryness, and rash.

In the open-label treatment phase, the most common TEAEs reported in the 769 patients with at least 6 months exposure to SANCTURA XR® were: constipation, and dry mouth. Urinary tract infection and rash was also reported in several patients, including one of each judged by the investigator to be possibly related to treatment. Several adverse events were reported as severe in the open-label treatment phase, including one urinary tract infection, two urinary retention events, and one aggravated constipation.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of trospium chloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal – gastritis; Cardiovascular – palpitations, supraventricular tachycardia, chest pain, syncope, "hypertensive crisis"; Immunological – Stevens-Johnson syndrome, anaphylactic reaction, angioedema; Nervous System – dizziness, confusion, vision abnormal, hallucinations, somnolence, and delirium; Musculoskeletal – rhabdomyolysis; General – rash.

7 DRUG INTERACTIONS

Trospium is metabolized by ester hydrolysis and excreted by the kidneys through a combination of tubular secretion and glomerular filtration. Based on in vitro data, no clinically relevant metabolic drug-drug interactions are anticipated with SANCTURA XR®. However, some drugs which are actively secreted by the kidney may interact with SANCTURA XR® by competing for renal tubular secretion.

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

7.1 Digoxin

Concomitant use of trospium chloride 20mg twice daily and digoxin did not affect the pharmacokinetics of either drug *[see Clinical Pharmacology (12.3)]*.

7.2 Antacid

While the systemic exposure of trospium on average was comparable with and without antacid containing aluminum hydroxide and magnesium carbonate, 5 out of 11 individuals in a drug interaction study demonstrated either an increase or decrease in trospium exposure, in presence of antacid. The clinical relevance of these findings is not known *[see Clinical Pharmacology (12.3)]*.

7.3 Metformin

Co-administration of 500 mg metformin immediate release tablets twice daily reduced the steady-state systemic exposure of trospium by approximately 29% for mean $AUC_{(0-24)}$ and by 34% for mean C_{max}. The effect of a decrease in trospium exposure on the efficacy of SANCTURA XR® is unknown. The steady-state pharmacokinetics of metformin were comparable when administered with or without 60 mg SANCTURA XR® once daily under fasted condition. The effect of metformin at higher doses on trospium PK is unknown *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C: There are no adequate and well-controlled studies of SANCTURA XR® in pregnant women. SANCTURA XR® should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during SANCTURA XR® treatment are encouraged to contact their physician.

Trospium chloride was not teratogenic at statistically significant levels in rats or rabbits administered doses up to 200 mg/kg/day. This corresponds to systemic exposures up to approximately 16 and 32 times, respectively (based on AUC), the clinical exposure at the maximum recommended human dose (MRHD) of 60 mg. However, in rabbits, one fetus in each of the three treated dose groups (1, 1, and 32 times the MRHD) demonstrated multiple malformations, including umbilical hernia and skeletal malformations. A no effect level for maternal and fetal toxicity was observed at levels approximately equivalent to the clinical exposure at the MRHD (20 mg/kg/day in rats and rabbits). No developmental toxicity was observed in the offspring of female rats exposed pre- and post-natally to up to 200 mg/kg/day.

8.2 Labor and Delivery

The effect of SANCTURA XR® capsules on labor and delivery is unknown.

8.3 Nursing Mothers

Trospium chloride (2 mg/kg orally and 50 mcg/kg intravenously) was excreted, to a limited extent (less than 1%), into the milk of lactating rats (primarily as parent compound). It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, SANCTURA XR® should be used during lactation only if the potential benefit justifies the potential risk.

8.4 Pediatric Use

The safety and effectiveness of SANCTURA XR® in pediatric patients have not been established.

8.5 Geriatric Use

Of 1165 patients in Phase 3 clinical studies of SANCTURA XR®, 37% (n=428) were ages 65 and over, while 12% (n=143) were ages 75 and over.

No overall differences in effectiveness were observed between those subjects aged 65 and over and younger subjects. In SANCTURA XR® subjects ages 65 and over compared to younger subjects, the following adverse reactions were reported at a higher incidence: dry mouth, constipation, abdominal pain, dyspepsia, urinary tract infection and urinary retention. In subjects ages 75 and over, three reported a fall and in one of them a relationship to the event could not be excluded.

8.6 Renal Impairment

Severe renal impairment (creatinine clearance less than 30 mL/minute) may significantly alter the disposition of SANCTURA XR®. In a study of immediate-release trospium chloride, 4.2-fold and 1.8-fold increases in mean $AUC_{(0-\infty)}$ and C_{max}, respectively, were detected in patients with severe renal impairment. Use of SANCTURA XR® is not recommended in patients with severe renal impairment *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*. The pharmacokinetics of trospium chloride have not been studied in patients with creatinine clearance ranging from 30-80 mL/min.

Trospium is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function.

8.7 Hepatic Impairment

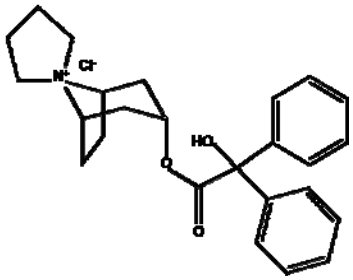
There is no information regarding the effect of severe hepatic impairment on exposure to SANCTURA XR®. In a study of patients with mild and with moderate hepatic impairment, given 40 mg of immediate-release trospium chloride, mean C_{max} increased 12% and 63%, respectively, and mean $AUC_{(0-\infty)}$ decreased 5% and 15%, respectively, compared to healthy subjects. The clinical significance of these findings is unknown. Caution is advised, however, when administering SANCTURA XR® to patients with moderate to severe hepatic impairment.

10 OVERDOSAGE

Overdosage with antimuscarinic agents, including SANCTURA XR®, can result in severe antimuscarinic effects. Supportive treatment should be provided according to symptoms. In the event of overdosage, ECG monitoring is recommended.

11 DESCRIPTION

SANCTURA XR® is an extended-release formulation of trospium chloride, a quaternary ammonium compound with the chemical name of Spiro [8-azoniabicyclo[3.2.1]octane-8,1'-pyrrolidinium], 3-[(hydroxydiphenylacetyl)oxy]-, chloride, (1α, 3β, 5α). The empirical formula of trospium chloride is $C_{25}H_{30}ClNO_3$ and its molecular weight is 427.97. The structural formula of trospium chloride is represented below:



Trospium chloride is a fine, colorless to slightly yellow, crystalline solid. The compound's solubility in water is approximately 1 g/2 mL.

SANCTURA XR® capsules contain 60 mg of trospium chloride, a muscarinic antagonist, for oral administration. Each capsule also contains the following inactive ingredients: sugar spheres, methacrylic acid copolymer, ethyl cellulose, hydroxypropyl methylcellulose, triethyl citrate, talc, and Opadry® white.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Trospium chloride is an antispasmodic, antimuscarinic agent.

Trospium chloride antagonizes the effect of acetylcholine on muscarinic receptors in cholinergically innervated organs including the bladder. Its parasympatholytic action reduces the tonus of smooth muscle in the bladder.

In vitro receptor binding studies have demonstrated the selectivity of trospium chloride for muscarinic over nicotinic receptors, and similar affinity for the M_2 and M_3 muscarinic receptor subtypes. M_2 and M_3 receptors are found in the bladder and may play a role in the pathogenesis of overactive bladder.

12.2 Pharmacodynamics

Placebo-controlled studies assessing the impact on urodynamic variables of an immediate-release formulation of trospium chloride were conducted in patients with conditions characterized by involuntary detrusor contractions. The results demonstrated that trospium chloride increases maximum cystometric bladder capacity and volume at first detrusor contraction.

Electrophysiology

The effect of 20 mg twice daily and up to 100 mg twice daily of an immediate-release formulation of trospium chloride on QT interval was evaluated in a single-blind, randomized, placebo and active (moxifloxacin 400 mg daily) 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. 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. The clinical significance of T-wave inversion in this study is unknown. This finding was not observed during routine safety monitoring in overactive bladder patients from 2 placebo-controlled clinical trials in 591 patients treated with 20 mg twice daily of immediate-release trospium chloride, nor was it observed in 2 placebo-controlled clinical trials in 578 patients treated with SANCTURA XR® capsules.

Also in this study, the immediate-release formulation of trospium chloride was associated with an increase in heart rate that correlated with increasing plasma concentration, with a mean elevation in heart rate compared to placebo of 9 beats per minute for the 20 mg dose and of 18 beats per minute for the 100 mg dose. In the two Phase 3 SANCTURA XR® trials the mean increase in heart rate compared to placebo was approximately 3 beats per minute in both studies.

12.3 Pharmacokinetics

Absorption: Mean absolute bioavailability of a 20 mg immediate-release dose is 9.6% (range 4.0-16.1%). Following a single 60 mg dose of SANCTURA XR®, peak plasma concentration (C_{max}) of 2.0 ng/mL occurred 5.0 hours post dose. By contrast, following a single 20 mg dose of an immediate-release formulation of trospium chloride, C_{max} was 2.7 ng/mL.

Effect of Food: Administration of SANCTURA XR® capsules immediately after a high (50%) fat-content meal reduced the oral bioavailability of trospium chloride by 35% for $AUC_{(0\text{-}Tlast)}$ and by 60% for C_{max}. Other pharmacokinetic parameters such as T_{max} and $t_{½}$ were unchanged in the presence of food.

A summary of mean (± standard deviation) pharmacokinetic parameters for a single dose of 60 mg SANCTURA XR® is provided in Table 3.

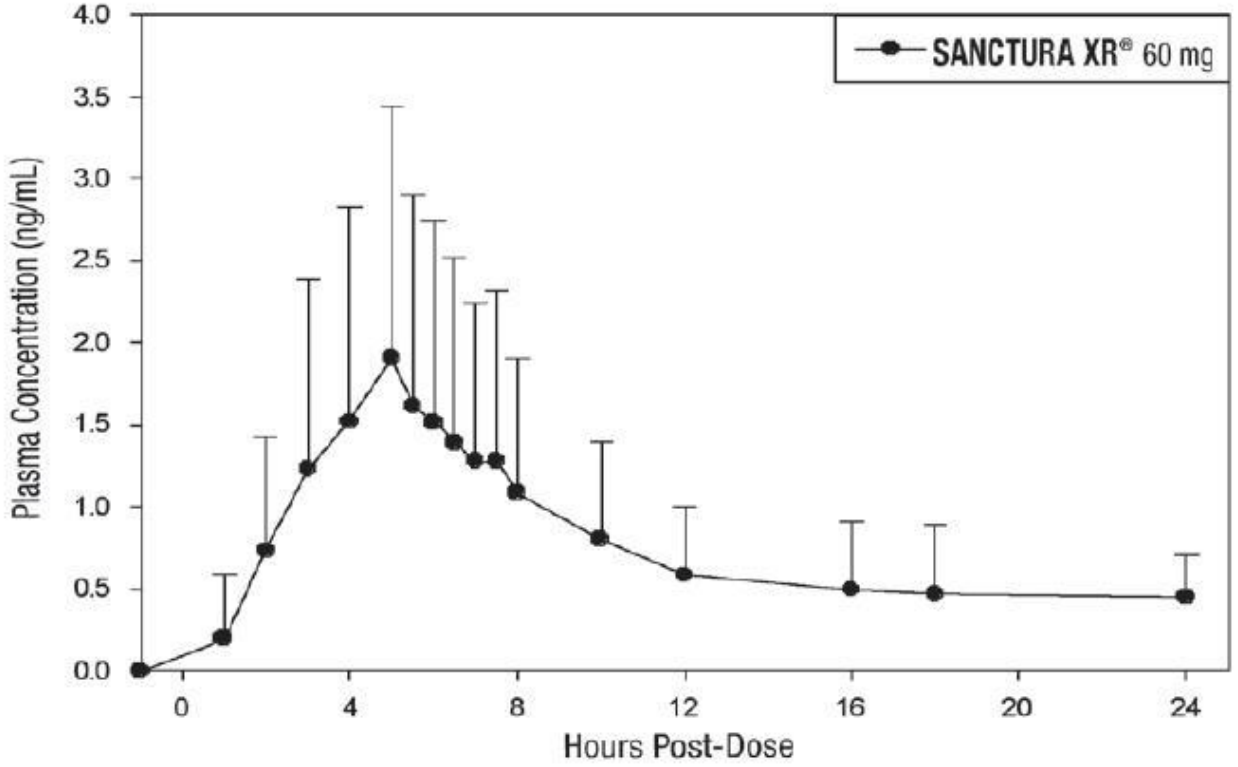
Table 3: Mean (±SD) Pharmacokinetic Parameter Estimates for a Single 60 mg Oral Dose of SANCTURA XR® in Healthy Volunteers

Treatment	**$AUC_{(0\text{-}24)}$** (ng•h/mL)	**C_{max}** (ng/mL)	**T_{max}** [a] (h)	**$t_{½}$** [b] (h)
SANCTURA XR® 60 mg	18.0 ± 13.4	2.0 ± 1.5	5.0 (3.0-7.5)	36 ± 22

[a] T_{max} expressed as median (range).
[b] $t_{½}$ was determined following multiple (10) doses.

The mean sample concentration-time (+ standard deviation) profile for SANCTURA XR® is shown in Figure 1.

Figure 1: Mean (+SD) Concentration-Time Profile for a Single 60 mg Oral Dose of SANCTURA XR® in Healthy Volunteers



Administration of SANCTURA XR® capsules immediately after a high (50%) fat-content meal reduced the oral bioavailability of trospium chloride by 35% for $AUC_{(0\text{-}Tlast)}$ and by 60% for C_{max}. Other pharmacokinetic parameters such as T_{max} and $t_{½}$ were unchanged in the presence of food. Coadministration with antacid had inconsistent effects on the oral bioavailability of SANCTURA XR®.

Distribution: Protein binding ranged from 50 to 85%, depending upon the assessment method used, when a range of concentration levels of trospium chloride (0.5-50 mcg/L) were incubated in vitro with human serum.

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

Trospium chloride is widely distributed, with an apparent volume of distribution >600 L.

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

Excretion: The plasma half-life for trospium following oral administration of SANCTURA XR® is approximately 35 hours. After oral administration of an immediate-release formulation of ^{14}C-labeled trospium chloride, a majority of the dose (85.2%) was recovered in feces and a smaller amount (5.8% of the dose) was recovered in urine. Of the radioactivity excreted into the urine, 60% was unchanged trospium.

The mean renal clearance for trospium (29.07 L/hour) is 4-fold higher than average glomerular filtration rate, indicating that active tubular secretion is a major route of elimination. There may be competition for elimination with other compounds that are also renally eliminated *[see Drug Interactions (7)]*.

Drug Interactions
Digoxin: Concomitant use of 20 mg **SANCTURA®** (trospium chloride immediate release) twice daily at steady state and a single dose of 0.5 mg digoxin in a crossover study with 40 male and female subjects did not affect the pharmacokinetics of either drug.

Antacid: A drug interaction study was conducted to evaluate the effect of an antacid containing aluminum hydroxide and magnesium carbonate on the pharmacokinetics of SANCTURA XR® (n=11). While the systemic exposure of trospium on average was comparable with and without antacid, 5 individuals demonstrated either an increase or decrease in trospium exposure, in presence of antacid.

Metformin: A drug interaction study was conducted in which SANCTURA XR® 60 mg once daily was co-administered with Glucophage® (metformin hydrochloride) 500 mg twice daily under steady-state conditions in 44 healthy subjects. Co-administration of 500 mg metformin immediate release tablets twice daily reduced the steady-state systemic exposure of trospium by approximately 29% for mean AUC_{0-24} and by 34% for mean C_{max}. The effect of decrease in trospium exposure on the efficacy of SANCTURA XR® is unknown. The steady-state pharmacokinetics of metformin were comparable when administered with or without 60 mg SANCTURA XR® once daily under fasted condition. The effect of metformin at higher doses on trospium PK is unknown.

Specific Populations
Age: In a phase 3 clinical trial of SANCTURA XR®, the observed plasma trospium concentrations were similar in older (greater than or equal to 65 years) and younger (less than 65 years) OAB patients.

Pediatric: The pharmacokinetics of SANCTURA XR® were not evaluated in pediatric patients.

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

Gender: Gender differences in pharmacokinetics of SANCTURA XR® have not been formally assessed. Data from healthy subjects suggests lower exposure in males compared to females.

Hepatic Impairment: There is no information regarding the effect of severe hepatic impairment on exposure to SANCTURA XR®. In a study of patients with mild (Child-Pugh score 5-6) and with moderate (Child-Pugh score 7-8) hepatic impairment, given 40 mg of immediate-release trospium chloride, mean C_{max} increased 12% and 63% respectively, and mean $AUC_{(0-\infty)}$ decreased 5% and 15%, respectively, compared to healthy subjects.

Renal Impairment: The pharmacokinetics of SANCTURA XR® in patients with severe renal impairment has not been evaluated. In a study of an immediate-release formulation of trospium chloride, 4.2-fold and 1.8-fold increases in mean $AUC_{(0-\infty)}$ and C_{max}, respectively, were detected in patients with severe renal impairment (creatinine clearance less than 30 mL/minute), compared with healthy subjects, along with the appearance of an additional elimination phase with a long half-life (~33 hours vs. 18 hours). Use of SANCTURA XR® is not recommended in patients with severe renal impairment *[see Dosage and Administration (2)]*. The pharmacokinetics of trospium chloride have not been studied in people with creatinine clearance ranging from 30-80 mL/min.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies with trospium chloride were conducted in mice and rats for 78 weeks and 104 weeks, respectively, at maximally tolerated doses. No evidence of a carcinogenic effect was found in either mice or rats administered up to 200 mg/kg/day (approximately 1 and 16 times, respectively (based on AUC), the expected clinical exposure levels at the maximum recommended human dose (MRHD) of 60 mg.

Mutagenesis: Trospium chloride was not mutagenic nor genotoxic in tests in vitro in bacteria (Ames test) and mammalian cells (L5178Y mouse lymphoma and CHO cells) or *in vivo* in the mouse micronucleus test.

Impairment of Fertility: No evidence of impaired fertility was observed in rats administered doses up to 200 mg/kg/day (about 16 times the expected clinical exposure at the MRHD, based on AUC).

14 CLINICAL STUDIES

SANCTURA XR® was evaluated for the treatment of patients with overactive bladder who had symptoms of urinary frequency, urgency and urge urinary incontinence in two 12-week, randomized, double-blind, placebo-controlled studies. For both studies, entry criteria required the presence of urge incontinence (predominance of urge), at least one incontinence episode per day, and 10 or more micturitions (voids) per day (assessed by 3-day urinary diary). Medical history and data from the baseline urinary diary confirmed the diagnosis. Approximately 88% of the patients enrolled completed the 12-week studies. The mean age was 60 years, and the majority of patients were female (84%) and Caucasian (86%).

The co-primary endpoints in the trials were the mean change from baseline to Week 12 in number of voids/24 hours (reductions in urinary frequency) and the mean change from baseline to Week 12 in number of incontinence episodes/24 hours. Secondary endpoints included mean change from baseline to Week 12 in volume per void.

Study 1 included 592 patients in both SANCTURA XR® 60 mg and placebo groups. As illustrated in Table 4 and Figures 2 and 3, SANCTURA XR® demonstrated statistically significantly ($p<0.01$) greater reductions in the urinary frequency and incontinence episodes, and increases in void volume when compared to placebo starting at Week 1 and maintained through Weeks 4 and 12.

Table 4: Mean (SE) Change from Baseline in Urinary Frequency, Urge Incontinence Episodes and Void Volume in Study 1

Efficacy Endpoint[a]	**Week**	**Placebo**	**SANCTURA XR®**	**P-Value**
Urinary frequency / 24 hours		**(N=300)**	**(N=292)**	
Mean Baseline	0	12.7 (0.2)	12.8 (0.2)	
Mean Change from Baseline	1	-1.2 (0.1)	-1.7 (0.1)	0.0092
	4	-1.6 (0.2)	-2.4 (0.2)	<0.0001
	12	-2.0 (0.2)	-2.8 (0.2)	<0.0001
Urge incontinence episodes / week		**(N=300)**	**(N=292)**	
Mean Baseline	0	29.0 (1.3)	28.8 (1.3)	
Mean Change from Baseline	1	-8.7 (1.0)	-13.0 (0.9)	0.0003
	4	-12.2 (1.1)	-16.5 (1.2)	0.0054
	12	-13.5 (1.1)	-17.3 (1.2)	0.0024

Efficacy Endpoint[a]	Week	Placebo	SANCTURA XR®	P-Value
Urinary volume / void (mL)		**(N=300)**	**(N=290)**	
Mean Baseline	0	155.9 (3.0)	151.0 (2.9)	
Mean Change from Baseline	1	12.1 (2.1)	21.6 (2.8)	0.0036
	4	17.2 (2.5)	30.0 (3.1)	0.0007
	12	18.9 (2.8)	29.8 (3.2)	0.0039

[a] treatment differences assessed by rank ANOVA for intent-to-treat population, last observation carried forward (ITT:LOCF) data set

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

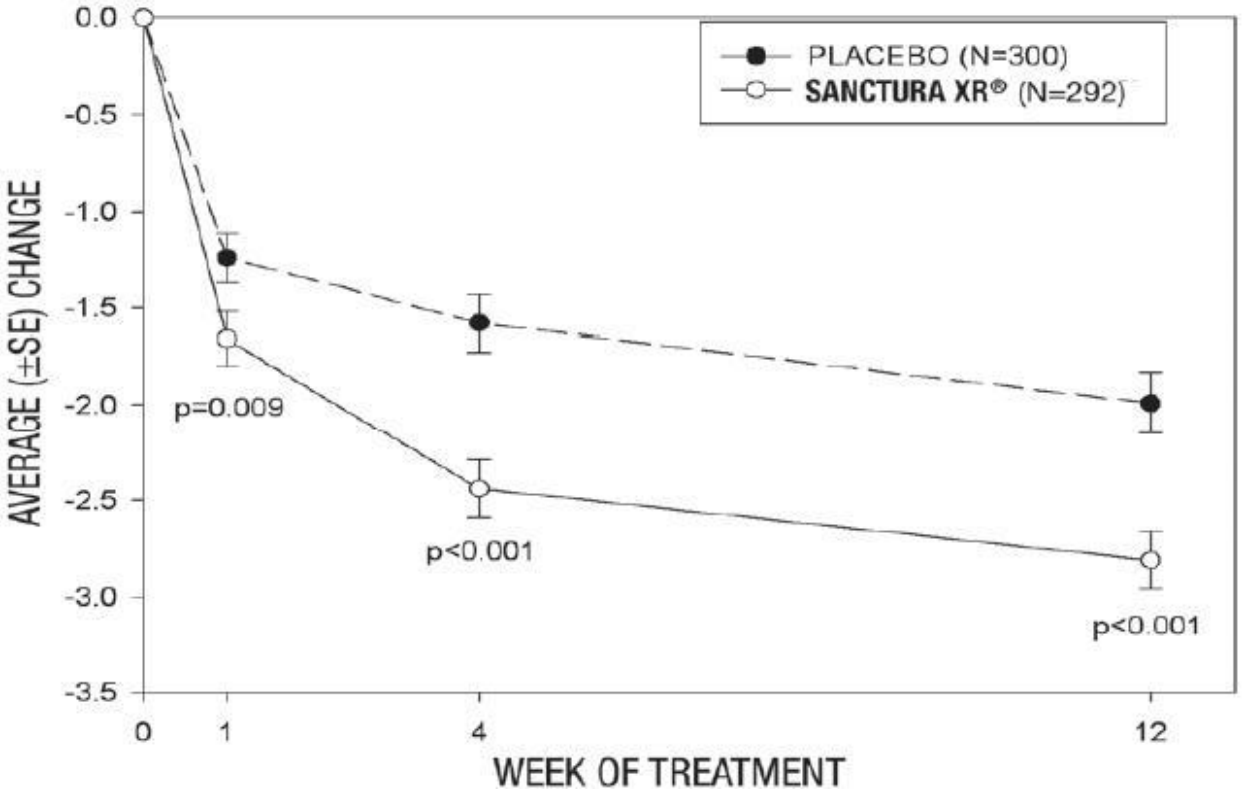
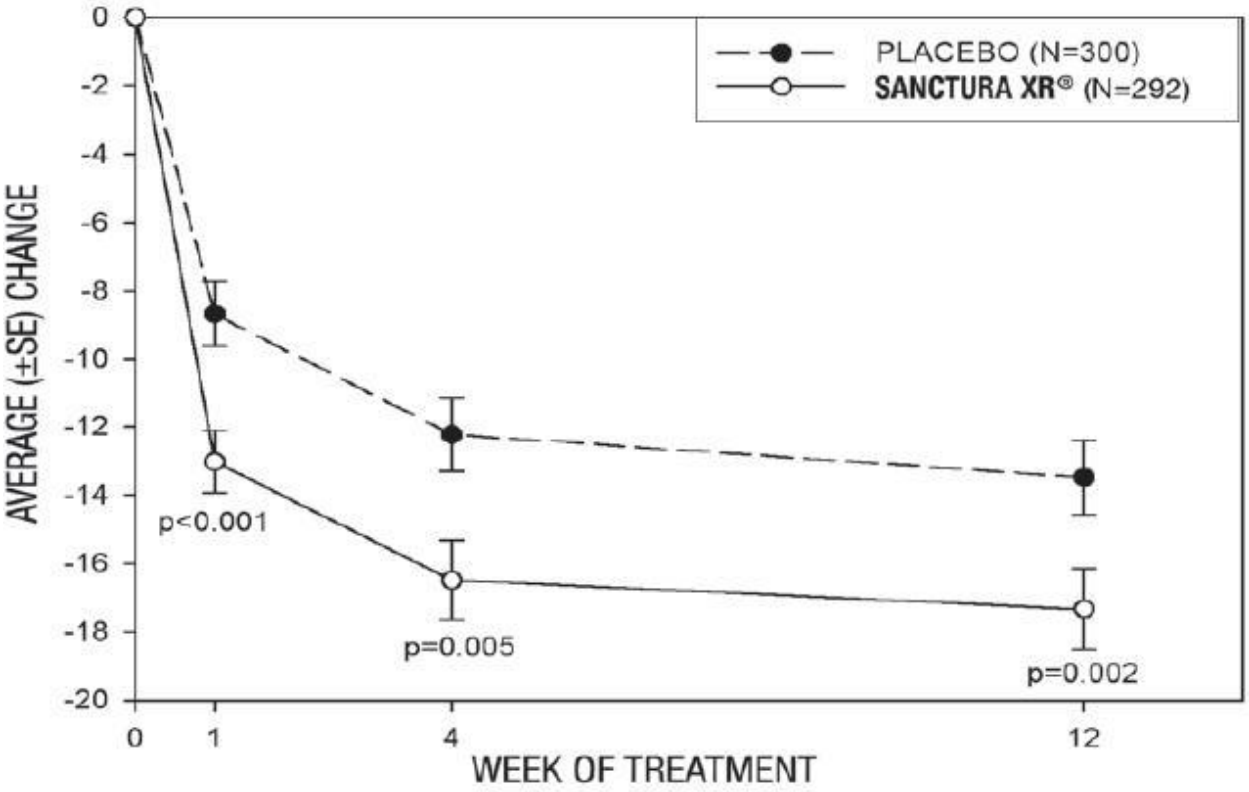


Figure 3: Mean Change from Baseline in Incontinence Episodes/Week by Visit: Study 1



Study 2 included 543 patients in both SANCTURA XR® 60 mg and placebo groups and was identical in design to Study 1. As illustrated in Table 5 and Figures 4 and 5, SANCTURA XR® capsules demonstrated statistically significantly ($p<0.01$) greater reductions in urinary frequency and incontinence episodes, and increases in void volume when compared to placebo at Weeks 4 and 12. However, at Week 1, statistically significant reductions were seen in urinary incontinence episodes and volume void only.

Table 5: Mean (SE) Change from Baseline in Urinary Frequency, Urge Incontinence Episodes and Void Volume in Study 2

Efficacy Endpoint[a]	Week	Placebo	SANCTURA XR®	P-Value
Urinary frequency / 24 hours		**(N=276)**	**(N=267)**	
Mean Baseline	0	12.9 (0.2)	12.8 (0.2)	
Mean Change from Baseline	1	-1.2 (0.2)	-1.4 (0.2)	0.0759
	4	-1.7 (0.2)	-2.3 (0.2)	0.0047
	12	-1.8 (0.2)	-2.5 (0.2)	0.0009
Urge incontinence episodes / week		**(N=276)**	**(N=267)**	
Mean Baseline	0	28.3 (1.4)	28.2 (1.2)	
Mean Change from Baseline	1	-7.3 (1.0)	-11.9 (1.0)	<0.0001
	4	-10.6 (1.1)	-15.8 (1.1)	<0.0001
	12	-11.3 (1.2)	-16.4 (1.3)	<0.0001
Urinary volume / void (mL)		**(N=276)**	**(N=266)**	
Mean Baseline	0	151.8 (2.8)	149.6 (2.9)	
Mean Change from Baseline	1	11.9 (2.5)	24.1 (2.4)	<0.0001
	4	19.6 (3.1)	29.3 (3.0)	0.0020
	12	17.8 (3.3)	31.5 (3.4)	0.0014

[a] treatment differences assessed by rank ANOVA for intent-to-treat population, last observation carried forward (ITT:LOCF) data set

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

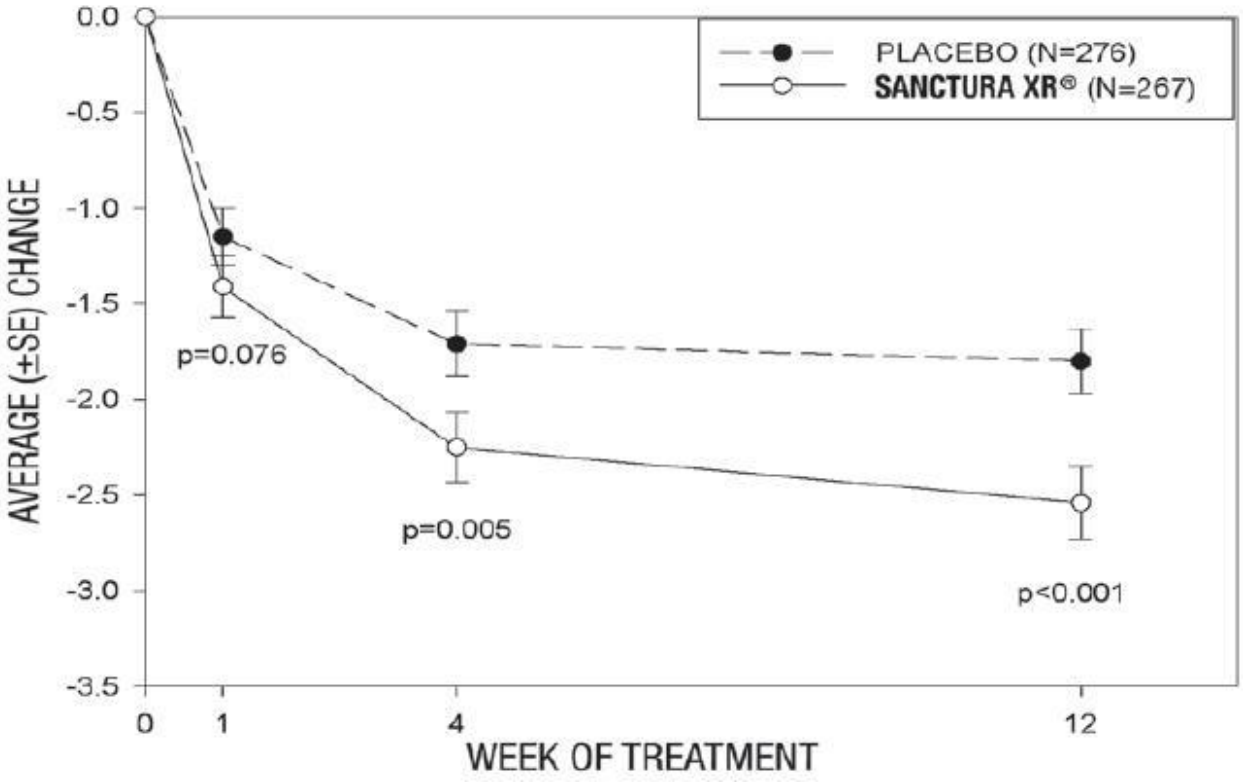
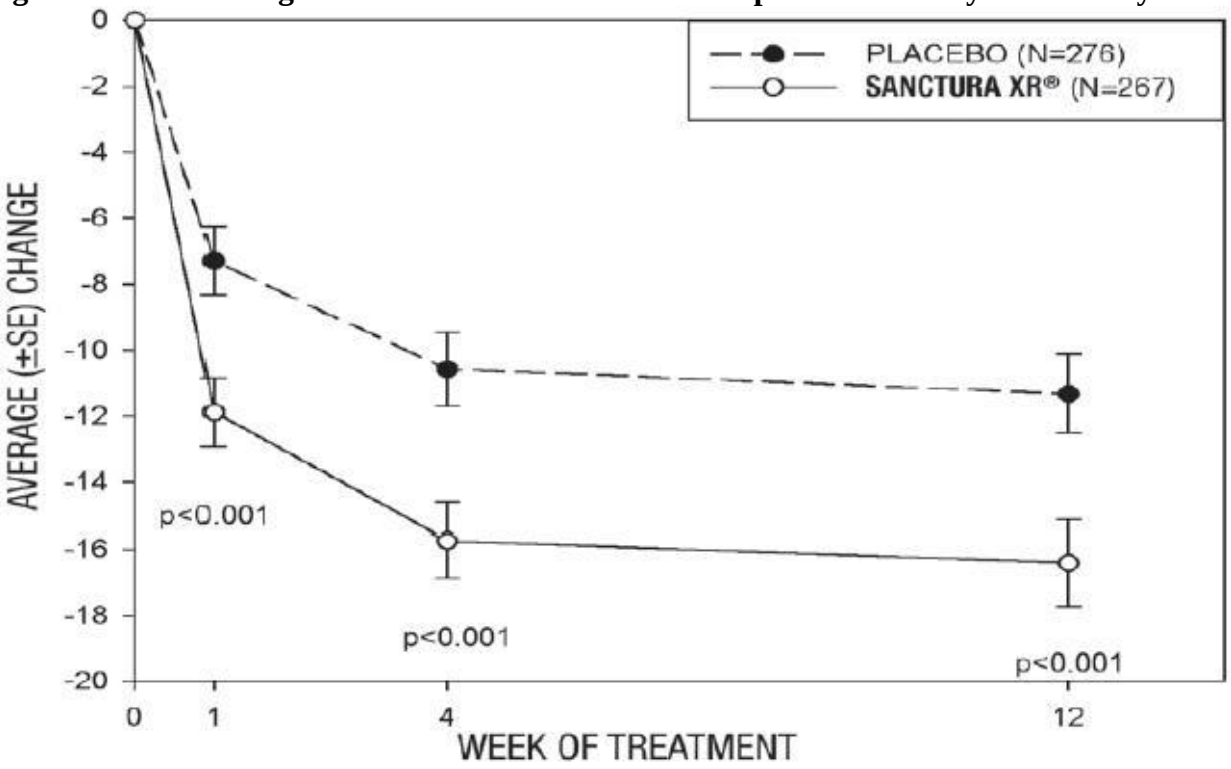


Figure 5: Mean Change from Baseline in Incontinence Episodes/Week by Visit: Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

SANCTURA XR® is supplied as 60 mg capsules (white opaque body and orange opaque cap, printed with SAN 60): 60 mg capsule, 30 count, HDPE bottle: NDC 0023-9350-30

Store at controlled room temperature 20° to 25°C (68° to 77°F). Excursion permitted at 15° to 30°C (see USP).

17 PATIENT COUNSELING INFORMATION

"See FDA-approved Patient Labeling (Patient Information)"

17.1 Angioedema

Patients should be informed that SANCTURA XR® may produce angioedema which could result in life-threatening airway obstruction. Patients should be advised to promptly discontinue SANCTURA XR® therapy and seek immediate medical attention if they experience edema of the tongue, edema of the laryngopharynx, or difficulty breathing.

17.2 When Not to Use

Prior to treatment, patients should fully understand the risks and benefits of SANCTURA XR®. In particular, patients should be informed not to take SANCTURA XR® capsules if they:

- have urinary retention;
- gastric retention;
- uncontrolled narrow-angle glaucoma;
- are allergic to any component of SANCTURA XR®.

17.3 Administration

Patients should be instructed regarding the recommended dosing and administration of SANCTURA XR®:

- Take one SANCTURA XR® capsule daily in the morning with water.
- Take SANCTURA XR® on an empty stomach or at least 1 hour before a meal.
- Use of alcoholic beverages within 2 hours of dosing with SANCTURA XR® is not recommended.

17.4 Adverse Reactions

Patients should be informed that the most common side effects with SANCTURA XR® are dry mouth and constipation and that other less common side effects include trouble emptying the bladder, blurred vision, and heat prostration. Because anticholinergics, such as SANCTURA XR®, may produce dizziness or blurred vision, patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effects have been determined. Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents.

Patient Information

SANCTURA XR® [*SANK-TOUR-AH EKS-AHR*]
(trospium chloride extended release capsules)

Read the Patient Information that comes with SANCTURA XR® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SANCTURA XR®?

SANCTURA XR® is a prescription medicine used to treat adults with overactive bladder who have the following symptoms:

- a strong need to urinate right away;
- leaking or wetting accidents due to a strong need to urinate right away;
- a need to urinate often.

Who should not take SANCTURA XR®?

Do not take SANCTURA XR® if you:

- have trouble emptying your bladder;
- have delayed or slow emptying of your stomach;
- have an eye problem called "uncontrolled narrow-angle glaucoma";
- are allergic to SANCTURA XR® or any of its ingredients. See the end of this leaflet for a complete list of ingredients.

SANCTURA XR® has not been studied in children under the age of 18 years.

What should I tell my doctor before starting SANCTURA XR®?

Tell your doctor about all of your medical conditions including if you:

- have any stomach or intestinal problems or problems with constipation;
- have trouble emptying your bladder or have a weak urine stream;
- have an eye problem called narrow-angle glaucoma;
- have kidney problems;
- have liver problems;
- are pregnant or planning to become pregnant. It is not known if SANCTURA XR® can harm your unborn baby.

- are breastfeeding. It is not known if SANCTURA XR® passes into breast milk and if it can harm your baby. You should talk to your doctor about the best way to feed your baby if you are taking SANCTURA XR®.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. SANCTURA XR® and certain other medicines can interact and make some side effects worse. SANCTURA XR® can affect how other medicines are handled by the body.
Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

How should I take SANCTURA XR®?
Take SANCTURA XR® exactly as prescribed.
- Take one SANCTURA XR® capsule daily in the morning with water.
- Take SANCTURA XR® on an empty stomach or at least 1 hour before a meal.
- Do not take alcohol within 2 hours of taking SANCTURA XR®.
- If you take too much SANCTURA XR®, call your local Poison Control Center or go to an emergency room right away.

What are the possible side effects of SANCTURA XR®?
SANCTURA XR® may cause allergic reactions that may be serious. Symptoms of a serious allergic reaction may include swelling of the face, lips, throat or tongue. If you experience these symptoms, you should stop taking SANCTURA XR® and get emergency medical help right away.

The most common side effects with SANCTURA XR® are:
- dry mouth;
- constipation.

SANCTURA XR® may cause other less common side effects, including:
- trouble emptying the bladder;
- blurred vision and drowsiness. Do not drive or operate heavy machinery until you know how SANCTURA XR® affects you.
- heat prostration. Due to decreased sweating, heat prostration can occur when drugs such as SANCTURA XR® are used in a hot environment.

Tell your doctor if you have any side effects that bother you or that do not go away.

These are not all possible side effects of SANCTURA XR®. For more information, ask your doctor, healthcare professional or pharmacist.

How should I store SANCTURA XR®?
- Keep SANCTURA XR® and all other medicines out of the reach of children.
- Store SANCTURA XR® at room temperature, 68° to 77°F (20° to 25°C).
- Safely dispose of SANCTURA XR® capsules that are out of date or that you no longer need.

General information about SANCTURA XR®
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use SANCTURA XR® for a condition for which it was not prescribed. Do not give SANCTURA XR® to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about SANCTURA XR®. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about SANCTURA

XR® that is written for health professionals. You can also call Allergan's product information department at 1-800-433-8871.

What are the ingredients in SANCTURA XR®?
Active Ingredient: trospium chloride.
Inactive Ingredients: sugar spheres, methacrylic acid copolymer, ethyl cellulose, hydroxypropyl methylcellulose, triethyl citrate, talc, and Opadry® white.

Manufactured for:
Allergan, Inc.
Irvine, CA 92612, U.S.A.

Manufactured by:
Catalent Pharma Solutions, Inc.
Somerset, NJ 08873, U.S.A.

Made in the U.S.A.