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APPLICATION NUMBER:
NDA 22-103

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Clinical Pharmacology
Division of Clinical Pharmacology 3
Tracking/Action Sheet for Formal/Informal Consults

From: Sandhya Apparaju

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified
IND/NDA submission

DATE: 07/16/2007

IND No.:
Serial No.:

NDA No.
22-103

DATE OF DOCUMENT
06/29/2007 and 07/11/2007

NAME OF DRUG
Sanctura XR (Trospium Chloride
modified Release Capsules)

PRIORITY CONSIDERATION

Date of informal/Formal
Consult:

NAME OF THE SPONSOR: Indevus Pharmaceuticals, Inc.

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- | | | |
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| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-
NDA/CMC/Pharmacometrics/Others) | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):
[NDA labeling negotiations] |
| <input type="checkbox"/> PHASE IV RELATED | | |

REVIEW ACTION

- | | | |
|---|---|---|
| <input type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with
Name: [] | <input checked="" type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | <input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes
dated: [] | <input type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox | | <input type="checkbox"/> See submission cover letter |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | | <input type="checkbox"/> OTHER (SPECIFY BELOW):
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REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

The following review summarizes OCP-relevant labeling negotiations for Sanctura XR:

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2 Page(s) Withheld

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/s/

Sandhya Apparaju
7/17/2007 09:31:06 AM
BIOPHARMACEUTICS

Myong-Jin Kim
7/17/2007 02:57:43 PM
PHARMACOLOGIST

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-103	Submission Date: 10/13/2006, 12/13/2006, 01/29/2007
Brand Name	Sanctura XR™
Generic Name	Trospium Chloride
Reviewer	Sandhya Apparaju
Team Leader	Myong Jin Kim
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Indevus Pharmaceuticals, Inc.
Relevant IND(s)	71,305
Relevant NDA	21-595
Submission Type; Code	Standard
Formulation; Strength(s)	Modified Release Capsules; 60 mg
Indication	Overactive Bladder

An optional inter-divisional CPB briefing was held on June 14th 2007 from 10-11 AM in conference room 3560 of White Oak Bldg 21. Attendees included Drs'. Hae Young Ahn, Myong Jin Kim, Mark Hirsch, Suresh Kaul, Harry Handelsman, Sandra Suarez, Donny Tran, Chongwoo Yu, Insook Kim, Srikanth Nallani, Ting Eng Ong and Sandhya Apparaju.

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1 Executive Summary

- In this new drug application (NDA 22-103), Indevus Pharmaceuticals, Inc. is seeking the approval of a new modified release (MR) formulation of trospium chloride, Sanctura XR™ 60 mg capsules for the treatment of Overactive Bladder (OAB). Trospium chloride is currently approved in U.S. as Sanctura® 20 mg immediate release (IR) tablets, for the same indication (NDA 21-595). The approved product is taken twice daily (BID). The proposed dosing frequency of the new Sanctura XR formulation (also referred to as the 'XR formulation' in this review) is once daily (QD) in the morning under fasted conditions. In support of this NDA, the sponsor has submitted results from two phase 1 pharmacokinetic (PK) studies in healthy volunteers, a phase 2 dose-confirming study, and two phase 3 clinical safety and efficacy trials in OAB patients. In addition, results from two pilot PK studies evaluating different prototypical formulations and an in vitro alcohol interaction study were submitted.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 22-103 to be acceptable provided that satisfactory agreement is reached between the sponsor and the agency regarding language in the package insert.

1.2 Phase IV Commitments

None

1.3 Summary of CPB Findings

- Definitive PK study IP631-020: Trospium from Sanctura XR 60 mg capsules was absorbed with a median T_{max} of 5 hours. Values of the peak drug concentrations (C_{max}) and area under the curve (AUC₀₋₂₄) were 1.8 ± 1.7 ng/ml and 20.2 ± 14.2 ng.h/ml, respectively. Trospium exposure following once daily 60 mg XR formulation was found to be lower compared to exposure following twice daily 20 mg IR formulation that had C_{max} and AUC₀₋₂₄ values of 2.7 ± 1.2 ng/ml and 30 ± 11.3 ng.h/ml, respectively.
- Drug accumulation (~ 1.5-fold) occurred after multiple daily dosing and steady-state was achieved by day 8; drug half-life from the XR formulation was extended compared to the approved IR formulation (36 h vs. 27 h).
- Steady-state trospium concentration-time profiles for the proposed 60 mg Sanctura XR™ formulation are shown in comparison to the approved Sanctura® 20 mg BID formulation:

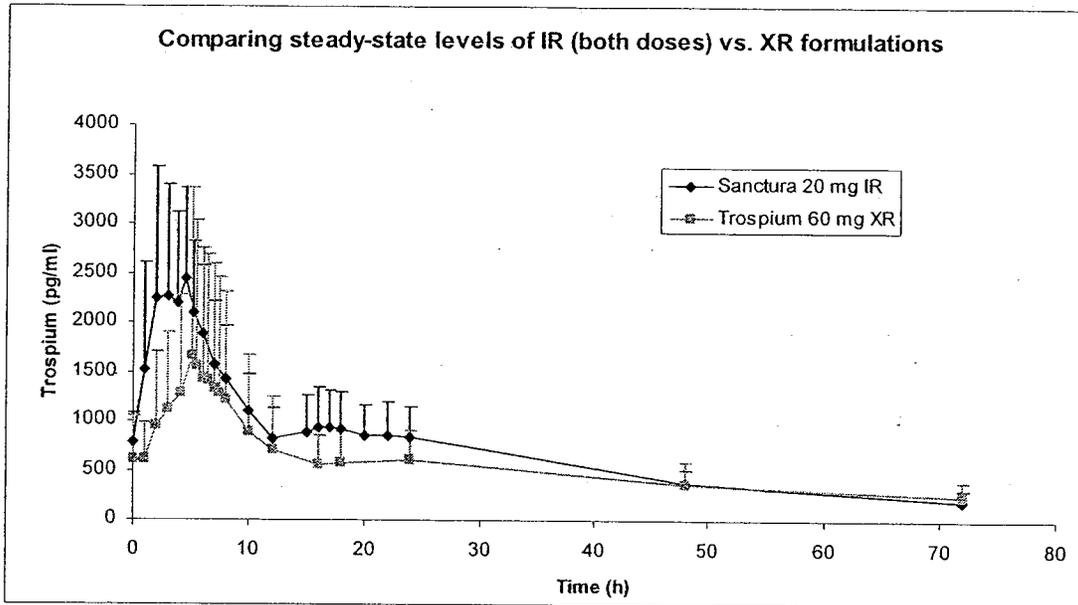


Figure 1: Steady-state plasma concentration-time profiles of trospium following the proposed XR and approved IR formulations in healthy volunteers (Mean \pm SD).

- This study also evaluated PK in geriatric subjects ($n = 11$; age ≥ 65) following once daily dosing for 10 days with a lower strength (30 mg) of the XR formulation. At this dose level, trospium systemic exposure was somewhat lower in geriatric subjects compared to younger (age < 65) subjects on 60 mg XR once daily (C_{max} lower by 22 % and AUC lower by 6 %).
- Food-effect study IP631-019: Dosing in presence of food reduced trospium C_{max} by 60% and AUC_{last} by 40%; therefore Sanctura XR is recommended to be dosed under fasted conditions; clinical trials were conducted under fasting conditions as well. The effect of antacid co-administration on trospium exposure from Sanctura XR was evaluated in this study but results were inconclusive.
- Phase 2 clinical trial IP631-016: In this parallel group, 2-week study in OAB patients, the safety and efficacy following two different dose regimens [morning (AM) vs. Evening (PM)] of Sanctura XR 60 mg was evaluated against placebo ($N = 50$ patients per group). Results of this study suggest superior efficacy (*i.e. change from baseline in the average volume voided per toilet void, and in the OAB-symptom composite score, OAB-SCS*) and better safety (lower frequency of anticholinergic side effects) of the AM regimen of the XR formulation compared to placebo and the PM regimen. This study did not conclusively address diurnal variability in trospium exposure from the XR formulation. Based on the safety and efficacy outcomes, the AM regimen of trospium was selected for further evaluation in phase 3 trials. The proposed label for Sanctura XR clearly indicates once daily dosing in the morning.
- Phase 3 clinical trial IP631-018: In this parallel group, double-blind, 12-week phase 3 clinical trial evaluating Sanctura XR 60 mg vs. placebo ($n = 300$ per group) in OAB patients, Sanctura XR demonstrated superiority compared to placebo in the co-primary end points of efficacy (*i.e. change in average number*

of toilet voids per day, and change in urge urinary incontinence (UUI) episode frequency per day).

- Trospium concentrations obtained by sparse sampling on day 8, 28 and 84 of the phase 3 clinical trial IP631-018 were pooled with concentrations from definitive PK study IP631-020, and the phase 2 study I631-016 to develop a population PK model; trospium PK parameters were predicted by the sponsor based on the model-simulated concentration-time profiles. The model predicted PK parameters in OAB patients were comparable to those obtained in the definitive PK study in healthy subjects.
- In general, the observed trospium plasma concentrations in the population PK database were similar across subgroups of interest including diagnosis (healthy vs. patient), renal function status, hepatic function status, age group (< 65 years vs. ≥ 65 years), and presence or absence of concomitant use of drugs that might alter renal blood flow or active renal secretion.
- Gender appeared to have a significant impact on trospium concentrations based on the results of the phase 1 PK study in which females demonstrated up to 2-fold higher exposure (both C_{max} and AUC) compared to males. Because OAB is predominant in females, safety and efficacy have been adequately characterized in this population during the two phase 3 clinical trials of Sanctura XR in which females comprised 85 % of the total enrolled patients.
- No new studies in renal impairment subjects were conducted for Sanctura XR. However, a special population study conducted for the approved IR product demonstrated significant increase in trospium exposure (C_{max} by 2-fold and AUC by 4.5 fold) in presence of severe renal impairment. Sanctura XR is therefore not recommended for use in presence of severe renal impairment.
- Hepatic impairment did not cause clinically relevant increases in trospium AUC from the IR product; currently there is no recommended dosage adjustment for the approved IR product. Because average trospium exposure from Sanctura XR is lower compared to the IR product given BID, no dosage adjustment is warranted in this special population.
- The release of trospium chloride from Sanctura XR was evaluated in presence of varying alcohol strengths (0, 10 %, 15 %, 20 %, 30 % and 40 %); drug release in vitro was significantly altered in presence of 40 % alcohol, with the entire dose being released within 2 hours as opposed to 12 hours in the absence of alcohol. Study results suggest potential for dose dumping in presence of high proof alcohol products and therefore will be addressed in the label using appropriate language to prevent dosing of Sanctura XR simultaneously with alcoholic beverages.
- Dissolution: Because the proposed XR formulation is comprised of _____, sponsor has proposed release specifications for each of these components as well as for the final capsule formulation. The proposed specifications for _____ and the final formulation involved a range of _____ around the average release rate; the sponsor was recommended to tighten the dissolution specifications to ±10 % or to a maximum range of 25 % (teleconference dated June 27, 2007) per the guidance. The Sponsor committed to reevaluating the release and stability data and agreed to submit a revised proposal for dissolution specifications based on this review.

2 QBR

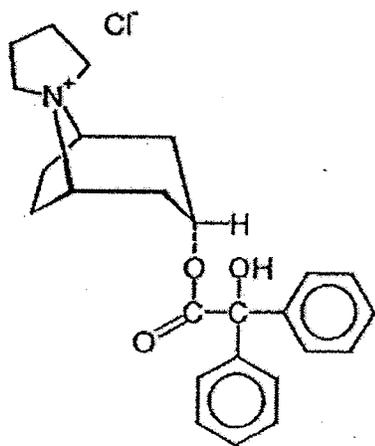
2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the Clinical Pharmacology and Biopharmaceutics of this drug?

- Trospium Chloride is currently approved in U.S. as Sanctura® 20 mg tablets (NDA 21-595; approved May 28, 2004). This immediate release formulation is taken BID under fasted conditions for the treatment of OAB. In NDA 22-103, sponsor is seeking approval of a new modified release formulation of trospium chloride for the same indication as the currently approved product. The proposed dosage regimen for Sanctura XR is 60 mg once daily in the morning under fasting conditions. In this NDA, the sponsor has submitted results from a phase II dose-confirming study, two phase III clinical safety and efficacy trials in OAB patients, a definitive PK study, a food effect and antacid interaction study, and in vitro alcohol interaction study. Special population studies were conducted for the approved IR product and were not repeated with the new formulation.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

- Drug Substance: The generic name for Sanctura™ is trospium chloride, a quaternary ammonium compound with chemical name of spiro[8-azoniabicyclo[3,2,1]octane-8,1'-pyrrolidinium]-3-[(hydroxydiphenyl-acetyl)-oxy]chloride(1 α , 3 β , 5 α)-(9Cl). The empirical formula of trospium chloride is C₂₅H₃₀ClNO₃. It has a molecular weight of 427.97.
- The structural formula of trospium chloride is represented in Figure 2.



Molecular formula: C₂₅H₃₀NO₃Cl

Figure 2: Structure of Trospium Chloride.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

- The recommended dosage of Sanctura XR is one 60-mg capsule taken orally once daily in the morning. Sanctura XR should be dosed with water on an empty stomach, at least one hour before a meal. Sanctura XR is not recommended for use in severe renal impairment patients.
- Dosage forms and strengths: Sanctura XR is supplied as 60 mg oral capsules.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology database for NDA 22-103 (Sanctura XR) consists of results from the following studies:

- IP631-009 (Pilot): A pilot, randomized, 6-way crossover bioavailability (BA) study of prototypic formulations in healthy adult female volunteers under fasting conditions; this study did not include the final proposed formulation.
- IP631-011 (Pilot PK study): An open-label, randomized, 5-way crossover pilot study in healthy volunteers (N = 25) to determine the PK of four once-daily prototypic formulations.
- IP631-019 (Food-effect study): A phase 1, single-dose, open label, randomized, 3-period, 3-arm crossover, BA study to assess the PK effect of food or co-administration of an antacid on Sanctura XR 60 mg; N = 12 healthy subjects.
- IP631-020 (Definitive PK study): A phase 1, multiple dose, randomized, open-label, 2-period, 2-arm crossover BA study in healthy adult subjects (n = 24; 18-55 years). Study characterized the steady state PK and compared the relative BA of trospium chloride and its major metabolite, azoniaspironortropanol from Sanctura XR 60 mg capsules QD vs. trospium chloride 20 mg IR tablets BID following 10 days of dosing on each regimen. This study also evaluated the steady state PK in geriatric subjects (n = 11; 65-80 years) following 10 days of dosing with Sanctura XR 30 mg capsules.
- IP631-016 (Phase 2): A parallel, randomized, double-blind, placebo-controlled, 2-week treatment trial in patients with OAB to compare two different dosing regimens (AM or PM dosing) of Sanctura XR 60 mg QD capsules and placebo; N = 49 on placebo, N = 50 on Sanctura XR AM dose and N = 49 on Sanctura XR PM dose.
- IP631-018 (Phase 3): A parallel, randomized, double-blind, placebo-controlled, 12-week treatment trial in patients with OAB, followed by an optional 9-month

open-label treatment phase. Treatments evaluated were an oral dose of Sanctura XR 60 mg QD in the morning and matching placebo. N = 600 patients; (age: 18 years and older); A population PK report based on this study as well as studies IP631-016 (Phase II) and IP631-020 (Phase I) was included.

- In addition, the clinical database contains results from a second phase 3 clinical trial IP631-022 identical in all aspects to the earlier clinical trial, except this study did not include population PK sampling.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The two co-primary efficacy variables assessed in the phase 3 clinical trials were based on patient urinary diary data collected over 3 days prior to the baseline, and week 1, 4 and 12 visits; these were:

- The change in average number of toilet voids per day
- The change in urge urinary incontinence (UUI) episode frequency per day.

The secondary efficacy variables, also based on averages of patient urinary diary data collected over 3 days prior to the baseline and each double-blind visit, are listed below:

- UUI episodes frequency per week
- Urgency severity associated with toilet voids (where urgency severity per toilet void is measured by the IUSS©)
- OAB Symptom Composite Score (OAB-SCS) per day
- Volume voided per toilet void (collected for 2 days)
- Urge frequency per day
- “Dry rate” for UUI outcome defined as no UUI episodes
- Stress incontinence episodes frequency per day
- Total incontinence episodes frequency per day (the sum of unique urge urinary and stress incontinence episodes)
- Total micturitions (the sum of unique toilet voids and UUI episodes) per day
- Normal void frequency outcome defined as an average of ≤ 8 toilet voids per day
- Complete responder rate outcome defined as an average of ≤ 8 toilet voids and no UUI episodes per day

Similar efficacy variables were assessed in the two week phase 2 clinical trial, but with the volume voided per toilet void as the primary endpoint; this endpoint was chosen to be primary due to prior experience (with the IR product) indicating the sensitivity of this variable to treatment differences and evidence of treatment effect after even a short duration of treatment.

2.2.3 Exposure-response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

IP631-016 (Phase 2):

- Sanctura XR 60 mg capsules and matching placebo were administered once daily in the morning (AM) or in the evening (PM) in patients with OAB (N = 49 Placebo, N = 50 Trospium AM, N = 49 Trospium PM);
- Two post-dose PK samples were obtained from patients at the end of 1 week (day 8) and at 2 weeks (day 15) for assessment of plasma trospium concentrations.
- Efficacy endpoints included the baseline-adjusted changes in volume voided per toilet void and the Overactive Bladder-Symptom Composite Score (OAB-SCS); Patient daily diary records capturing voiding, incontinence, and urgency data, patient global assessment (OAB-PGA) were used to assess efficacy. The key efficacy analysis focused on the change from Baseline to Week 2 visit.
- The AM regimen of Sanctura 60 mg XR demonstrated superior efficacy over the placebo and the PM regimens, with regard to the two PD outcomes evaluated: change (increase) from baseline in the average volume voided per toilet void (primary) and the change (decrease) from baseline in the OAB-SCS score (secondary).
- In addition, with the AM regimen, the therapeutic effect of trospium was apparent within the first week of treatment and the response further increased in magnitude by the end of study (week 2); On the other hand, the PM regimen did not show demonstrable efficacy during the first week, but resulted in treatment effect at week 2.
- Linear regression of the concentration - response data from the AM regimen also demonstrated a significant correlation of trospium concentrations with changes in the efficacy endpoints, suggesting a treatment effect. This correlation reached statistical significance for the secondary endpoint (OAB-SCS).
- Similar relationship between plasma concentrations and response could not be confirmed for the PM regimen of Sanctura XR.

Table 2: Primary efficacy endpoint (change from baseline in average volume voided (ml) per toilet-void)

Mean change Efficacy Endpoint	Placebo AM		Placebo PM		Sanctura XR: AM		Sanctura XR: PM	
	Week 1	Week2	Week 1	Week2	Week 1	Week 2	Week 1	Week 2
Change from baseline in volume voided	7.12	15.31	16.66	20.83	22.73	29.54	8.02	21.66
% change from baseline in volume voided	4.53	9.66	11.7	15.2	18.35	21.08	9.48	17.86
Median change								
Change from baseline in volume voided	0.73	8.01	10.47	1.57	11.42	31.22	-0.595	16.22
% change from baseline in volume voided	0.77	8.45	5.85	1.39	8.67	15.78	-0.44	9.89

Table 3: Secondary efficacy endpoint (change from baseline in the OAB-symptom composite score)

Efficacy Endpoint	Placebo AM		Placebo PM		Sanctura XR: AM		Sanctura XR: PM	
	Week 1	Week 2	Week 1	Week 2	Week 1	Week 2	Week 1	Week 2
Change from baseline in OAB-SCS	-3.527	-4.51	-6.94	-8.56	-7.39	-10.11	-5.6	-7.56
% change from baseline in OAB-SCS	-9.658	-12.09	-14.37	-18.19	-18.24	-26.55	-15.8	-21.55
Median change								
Change from baseline in OAB-SCS	-4.14	-3.28	-3.57	-8.14	-6.71	-11.28	-6.07	-7.35
% change from baseline in OAB-SCS	-10.4	-10.26	-14.04	-24.4	-17.96	-32.64	-17.33	-21.3

AM Trospium 60 mg QD for 2 weeks

PM Trospium 60 mg QD for 2 weeks

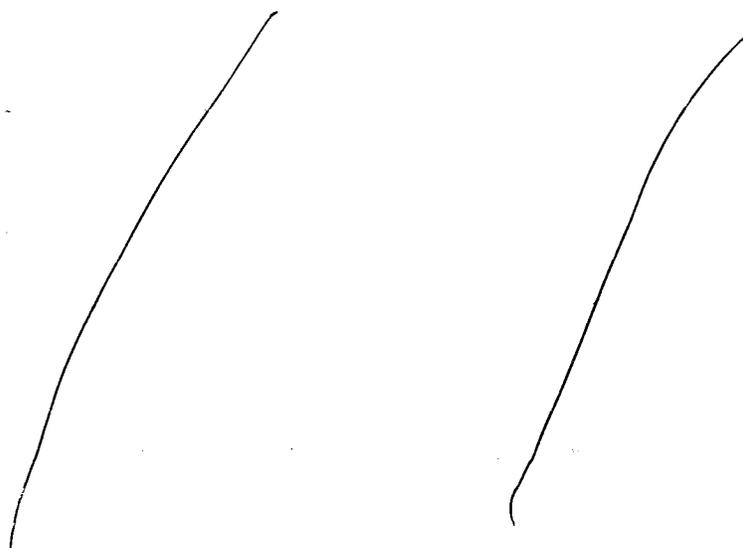


Figure 3: Exposure-response relationships from study IP631-016

2.2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

- While the overall incidence of adverse events (AE) was similar for the AM and PM Sanctura XR regimens in the phase 2 study IP631-016, the incidence of dry mouth and constipation was greater in the Trospium PM group.

Table 4: Adverse event frequency from phase 2 study IP631-016

MedDRA System organ class/preferred term	Number of patients (%)		
	Placebo N = 49	Trosipium Morning N = 50	Trosipium Evening N = 49
Total patients with at least 1 TEAE	10 (20.4)	18 (36.0)	18 (36.7)
Gastrointestinal disorders	6 (12.2)	10 (20.0)	15 (30.6)
Dry mouth	4 (8.2)	6 (12.0)	11 (22.4)
Constipation	0	1 (2.0)	8 (16.3)
Infections and infestations	0	3 (6.0)	1 (2.0)
Nervous system disorders	2 (4.1)	3 (6.0)	3 (6.1)
Headache	1 (2.0)	3 (6.0)	3 (6.1)

TEAE = treatment-emergent adverse event.
Reference: Appendix 17.2 Tables 9.3.1.2 and 9.3.1.6

- In the phase 3 clinical trial IP631-018, the overall incidence of adverse events was greater with Sanctura XR compared to placebo as shown in the table below; While constipation and dry mouth were the events reported with the highest incidence, the actual reported incidence for these events is stated to be lower than had been observed in studies involving the IR formulation (20 mg BID).

Table 5: Adverse event frequency in the phase 3 clinical trial IP631-018

MedDRA Preferred term	Number of patients (%)	
	Placebo N = 303	Trosipium N = 298
Total patients with at least 1 TEAE	147 (48.5)	170 (57.0)
Constipation	5 (1.7)	29 (9.7)
Dry mouth	9 (3.0)	26 (8.7)
Urinary tract infection	12 (4.0)	18 (6.0)
Tachycardia	1 (0.3)	4 (1.3)
Headache	12 (4.0)	4 (1.3)
Dry eye	2 (0.7)	4 (1.3)
Urinary retention	1 (0.3)	4 (1.3)
Rash	0 (0.0)	4 (1.3)
Blurred vision	2 (0.7)	3 (1.0)
Myocardial ischemia	0 (0.0)	1 (0.3)
Dizziness	5 (1.7)	1 (0.3)
Age-indeterminate myocardial infarction	1 (0.3)	0 (0.0)

TEAE = treatment-emergent adverse event.
Reference: Section 14.3 Table 9.3.1.2

While the overall AE frequency in geriatric patients was comparable to younger OAB patients, a higher incidence for constipation, urinary tract infections (UTI), and dyspepsia was observed in the patients ≥ 65 years (compared to patients < 65 years) in the phase 3 clinical trial:

Table 6: Adverse event frequency in the phase 3 trial stratified by age group

MedDRA Preferred term	Number of patients (%)			
	Placebo N = 303		Trospium N = 298	
	< 65 years (N=193)	≥ 65 years (N=110)	< 65 years (N=184)	≥ 65 years (N=114)
Total patients with at least 1 TEAE	96 (49.7)	51 (46.4)	111 (60.3)	59 (51.8)
Constipation	2 (1.0)	3 (2.7)	13 (7.1)	16 (14.0)
Dry Mouth	8 (4.1)	1 (0.9)	16 (8.7)	10 (8.8)
Urinary tract infection	7 (3.6)	5 (4.5)	6 (3.3)	12 (10.5)
Upper respiratory tract infection	10 (5.2)	6 (5.5)	6 (3.3)	2 (1.8)
Dyspepsia	3 (1.6)	0 (0.0)	2 (1.1)	6 (5.3)

TEAE = treatment-emergent adverse event.
Reference: Section 14.3 Table 9.3.1.23

- Sponsor's analysis of the phase 3 database suggested statistically significant relationships ($p < 0.004$) between exposure (both $AUC_{(0-24)}$ and C_{max}) and two of the three safety outcomes (dry mouth and constipation) for all subjects.
- A doubling of trospium exposure (AUC) was associated with an 80% increase in the risk of dry mouth (OR=1.8, 95% CI: 1.2 - 2.9) and a 120% increase in the risk of constipation (OR=2.2, 95% CI: 1.4 - 3.4). There was a slight, but non-statistically significant, elevation in the incidence of abdominal distension, discomfort, or pain with increased exposure (OR=1.2, $p > 0.23$).

2.2.3.3 Does this drug prolong the QT or QTc interval?

- Thorough QT study conducted for the IR formulation (NDA 21-595) did not show QT interval prolongation at therapeutic (20 mg BID) and supra-therapeutic doses (80 mg BID).

2.2.4 Pharmacokinetics

Study IP631-020:

- Single dose and steady-state PK of trospium and its inactive major metabolite azoniaspironortropanol (Azo) from 60 mg Sanctura XR were assessed in 24 healthy male and female volunteers.
- Steady-state PK of trospium from Sanctura XR was compared to that observed following twice daily dosing of the approved IR formulation (Sanctura® 20 mg).

2.2.4.1 What are the single dose and multiple dose PK parameters?

- Trospium was absorbed with a median T_{max} of 5.0 hours following once daily oral doses of Sanctura XR 60 mg administered in the morning, under fasted conditions.

- The half-life of trospium from the XR formulation was approximately 35 h.
- Steady state was reached by day 8 following daily dosing with trospium chloride 60 mg XR and drug accumulation at steady state was 1.4- and 1.5-fold for C_{max} and AUC(0-24), respectively.
- The inter-individual variability (% CV) in steady-state trospium PK was high (57.0 % to 89.9 %) with the XR formulation compared to the IR formulation (35-45 %).
- The single dose and steady-state trospium PK [mean ± SD (% CV)] following Sanctura XR 60 mg and the steady-state PK from Sanctura 20 mg BID (approved IR product) are shown:

Table 7: Single dose and multiple dose plasma pharmacokinetics of trospium [arithmetic mean ± SD (%CV)] following once daily dosing with Sanctura XR shown in relation to steady-state PK of the approved IR formulation (20 mg BID)

	T _{max} (h)	C _{max} (pg/ml)	C _{min} (pg/ml)	Half-Life (h)	AUC ₍₀₋₂₄₎ (pg.h/ml)	AUC _{last} (pg.h/ml)	AUC _{inf} (pg.h/ml)
Day 1: Sanctura XR 60 mg	5.00 (3.00-7.50)	2041 ± 1516 (74.3 %)	-	-	18020 ± 13418 (74.4 %)	18020 ± 13418 (74.4 %)	-
Day 10: Sanctura XR 60 mg	5.00 (0-7.50)	1873 ± 1683 (89.9 %)	418.6 ± 185.7 (44.4 %)	35.8 ± 22.37 (62.5 %)	20160 ± 14166 (70.3 %)	40660 ± 22825 (56.1 %)	45130 ± 15973 (35.4 %)
Day 10: Sanctura 20 mg BID (Reference)	4.50 (2.00-6.00)	2715 ± 1219 (44.9 %)	691.3 ± 246.9 (35.7 %)	27.2 ± 12.07 (44.4 %)	30020 ± 10644 (35.5 %)	47770 ± 19337 (40.5 %)	58410 ± 19857 (34.0 %)

Note: To facilitate 24 h exposure comparisons of the once daily XR vs. twice daily IR formulations, AUC parameters from the AM and PM doses of the IR tablet were combined accordingly; C_{max} was the greater of the two estimates between AM and PM dosing; T_{max} and C_{min} are reported from the same dosing interval from which C_{max} was selected; T_{max}: median (range);

- Trospium exposure from the 60 mg XR product was significantly lower when compared with the exposure from trospium chloride 20 mg BID dose group as shown from statistical comparison of geometric mean values:

Table 8: Statistical comparison of systemic steady state exposure from the proposed XR (treatment A) and approved IR (treatment B) formulations of trospium

Parameter	N	Treatment	Geometric Least-Squares Mean	Pairwise comparisons		
				Pair	Ratio (%)	90% CI
AUC ₍₀₋₂₄₎ (pg ^h /mL)	22	A	17360			
	23	B	28590	A/B	60.7	(51.1, 72.2)
AUC _(0-7.5h) (pg ^h /mL)	20	A	37790			
	23	B	43920	A/B	86.0	(71.6, 103.4)
C _{max} (pg/mL)	22	A	1517			
	23	B	2502	A/B	60.6	(48.7, 75.4)

- Metabolite PK: Plasma concentrations of the major metabolite were significantly lower following multiple dosing with the proposed 60 mg XR formulation in comparison to those observed with the approved IR formulation (20 mg BID):

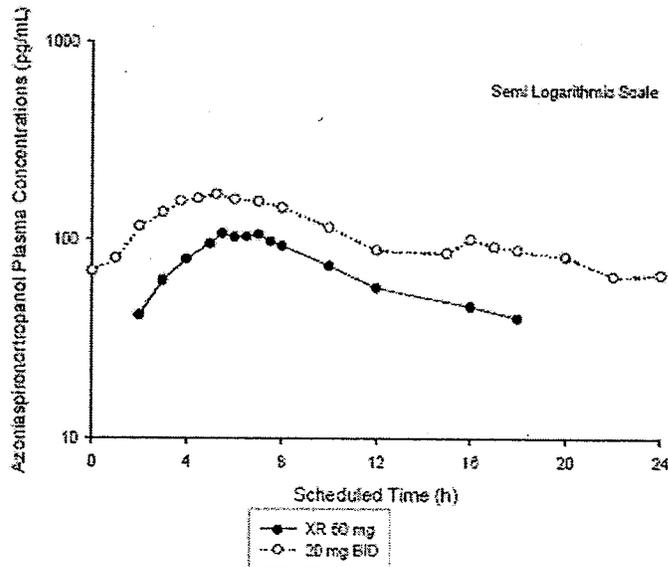


Figure 4: Steady-state metabolite concentration-time profiles following the proposed (XR) and approved (IR) formulations of trospium chloride.

Table 9: Pharmacokinetics of the inactive major metabolite, Azoniaspironortropanol

Treatment	AUC _(0-12h) (pg* ^h /mL)	AUC ₍₀₋₂₄₎ (pg* ^h /mL)	C _{max} (pg/mL)	T _{max} ^[a] (h)	t _{1/2} (h)
A (trospium chloride 60 mg XR QD)	1726 (1406)	2183 (979)	141.4 (76.0)	6.50	12.86 (6.79)
B (trospium chloride 20 mg BID)	2856 (2085)	2534(1206)	185.7 (84.5)	5.25	15.84 (7.71)

All values except those of T_{max} values reported as arithmetic mean (SD). SD = standard deviation; ^[a]T_{max} expressed as median.

Table 10: Statistical comparison of metabolite PK

Parameter	N	Treatment	Geometric Least-Squares Mean	Pairwise comparisons		
				Pair	Ratio (%)	90% CI
AUC ₍₀₋₂₄₎ (pg* ^h /mL)	13	A	1469			
	23	B	2192	A/B	67.0	(58.6, 76.6)
AUC _(0-12h) (pg* ^h /mL)	18	A	933.8			
	23	B	2229	A/B	41.9	(31.3, 56.1)
C _{max} (pg/mL)	19	A	120.6			
	23	B	168.7	A/B	71.5	(60.4, 84.6)

Note: Treatment A: XR capsules 60 mg QD (proposed); Treatment B: IR tablets 20 mg BID (approved)

- PK data from n =11 geriatric subjects dosed with 30 mg XR formulation suggested a comparable Tmax and T1/2 relative to a younger population; trospium exposure was somewhat lower (22 % lower Cmax and 6 % lower AUC) compared to the PK following 60 mg XR in healthy young volunteers.

Table 11: Trospium steady-state PK in geriatric subjects following once daily dosing with 30 mg XR shown in comparison to the 60 mg XR formulation.

Treatment	AUC _(0-∞) (pg·h/mL)	AUC _(0-Tmax) (pg·h/mL)	AUC ₍₀₋₂₄₎ (pg·h/mL)	C _{max} (pg/mL)	T _{max} [s] (h)	t _{1/2} (h)	HVD (h)
A (trospium chloride 60 mg XR)	45130 (15973)	40660 (22825)	20160 (14166)	1873 (1683)	5.00	35.78 (22.37)	13.25 (15.29)
C (trospium chloride 30 mg XR)	40980 (20279)	35910 (16608)	19070 (9292)	1456 (790)	5.50	31.01 (10.72)	14.57 (10.38)
	91 ^b	88 ^b	95 ^b	78 ^b	110 ^b	87 ^b	110 ^b

Values represent Mean (SD), ^a median T_{max}, ^b Trt C/Trt A, HVD: half-value duration i.e. duration over which plasma concentrations remain at greater than 50 % of the observed C_{max}.

2.2.4.2 How does the PK of the drug in healthy volunteers compare to that in patients?

- Sparse sampling for population PK analysis was conducted on day 8, 28 and 84 of the phase 3 clinical trial IP631-018 (18-84 years). Model-derived steady state PK parameters from the clinical trial patients were comparable to the C_{max} and AUC observed in healthy volunteers of the definitive PK study.

Table 12: Model-derived trospium PK parameters in patients dosed with once daily Sanctura XR 60 mg shown in comparison with PK from healthy volunteers.

Parameter	Phase 3 (Model-derived; Patient)	Phase 1 (Healthy)
C _{max} (pg/ml)	1529 ± 1339	1873 ± 1683
AUC ₀₋₂₄ (pg.h/ml)	23333 ± 15980	20160 ± 14166

- The overall distribution of plasma trospium concentrations in OAB patients (IP631-018) vs. healthy volunteers (IP631-020) was found to be comparable as shown in the figure below; while, there were few more outliers (from n = 6 phase 3 patients vs. n =1 phase 1 volunteers with concentrations > 7500 pg/ml) and few extreme outliers (n = 3 elderly female patients with trospium concentrations > 10,000 pg/ml) within the clinical trial population, higher exposure in such patients could not be correlated exclusively with any particular covariate of interest including renal or hepatic function status or use of concomitant medications.

IP631-020 (Healthy Volunteers);
n = 823 observations

IP631-018 (OAB Patients);
n = 1005 observations

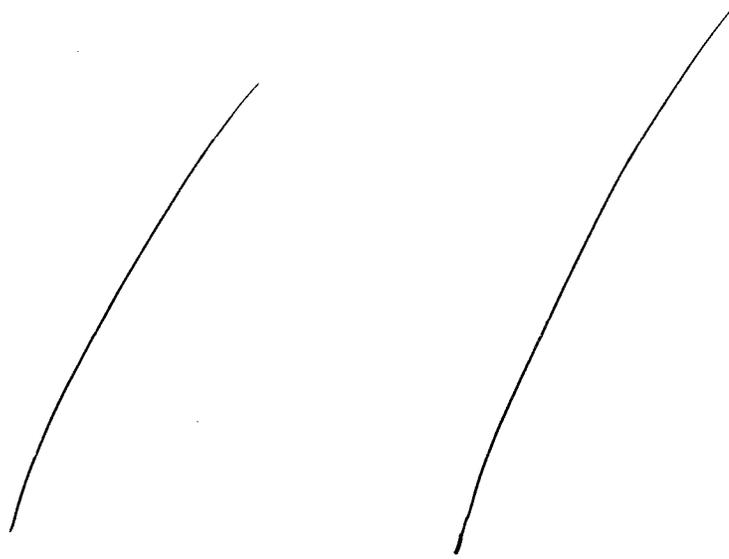


Figure 5: Comparison of observed trospium concentrations from OAB patients and healthy volunteers.

- In addition, available population data from the phase 3 clinical trial suggests that trospium exposure is comparable between younger vs. elderly patients following once daily dosing with 60 mg XR:

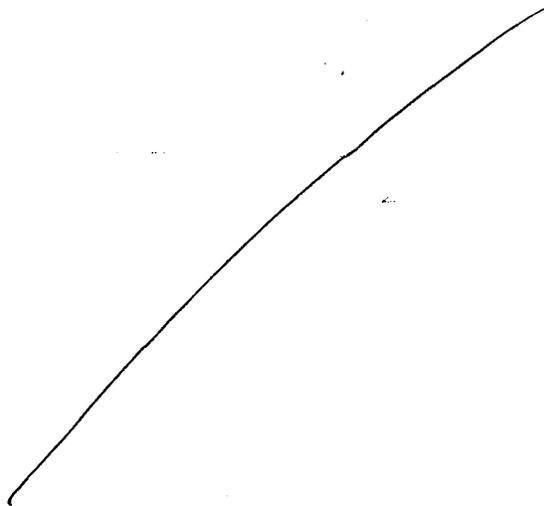


Figure 6: Trospium concentrations across age groups following once daily dosing with Sanctura XR 60 mg in the phase 3 clinical trial IP631-018.

2.2.4.3 What are the characteristics of drug absorption?

- Mean absolute BA of a 20 mg IR 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 (median) post dose. Steady-state concentrations were achieved by day 8 of once daily dosing with Sanctura XR in the morning, under fasted conditions.
- Food-effect on absorption: Administration of Sanctura XR immediately after a high fat meal reduced the oral BA of trospium chloride by 35% for AUC_{last} and by 60% for C_{max} . T_{max} and $T_{1/2}$ were unchanged in the presence of food. Phase 3 clinical trials were conducted under fasted conditions.

2.2.4.4 What are the characteristics of drug 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. Trospium chloride is highly distributed with an apparent volume of distribution > 600 L.

2.2.4.5 What are the characteristics of drug 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. Cytochrome 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 cytochrome P450 isoenzyme substrates (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4), suggest a lack of inhibition at clinically relevant concentrations.

2.2.4.6 What are the characteristics of drug excretion?

- The plasma half-life for trospium following oral administration of Sanctura XR is approximately 35 hours. After administration of oral ^{14}C -trospium chloride, the majority of the dose (85.2%) was recovered in feces and a smaller amount (5.8% of the dose) was recovered in urine; 60% of the radioactivity excreted in urine was unchanged trospium. 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 for trospium. There may be competition for elimination with other compounds that are also renally eliminated.

2.2.4.7 How do the PK parameters change with time following chronic dosing?

- Steady-state concentrations of trospium are achieved by day 8 of multiple daily dosing with Sanctura XR under fasted conditions. Some drug accumulation

occurs with daily dosing (1.4-fold). T_{max} and T_{1/2} do not appear to change with multiple daily dosing.

2.2.4.8 What is the inter-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

- Within the healthy volunteers of the definitive PK study, the inter-individual variability (% CV) in steady state trosipium PK from Sanctura XR was high (57 % to 89.9%). Female volunteers exhibited higher exposure compared to males; moreover, the % CV was higher in females compared to males: C_{ss,max} (86 % vs. 55 %), and AUC (66 % vs. 38%).
- The variability of the model-predicted trosipium PK parameters in the OAB patients was comparable (CV: 68-88 %) to that observed in healthy volunteers; exposure in patients is likely to be influenced by the presence of renal or hepatic impairment and theoretically by the concomitant use of drugs affecting active renal secretion.
- Because CYP450 enzymes are not involved in the elimination of trosipium, concomitant use of drugs that are CYP450 substrates, inhibitors or inducers is not expected to influence trosipium exposure.
- Age group (< 65 years vs. ≥ 65 years) did not influence trosipium steady state concentrations as suggested by observed concentrations in the phase 3 clinical trial for Sanctura XR and also based on data submitted to NDA 21-595 for the approved IR product.
- Population PK analysis of the phase 3 data suggested body surface area to be a significant covariate that was inversely correlated to trosipium clearance. No other covariates of interest including age, gender, concomitant medication use, renal impairment etc., were found to reduce variability of the model-predicted PK parameters in this analysis.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? Are there any proposed dosage adjustments?

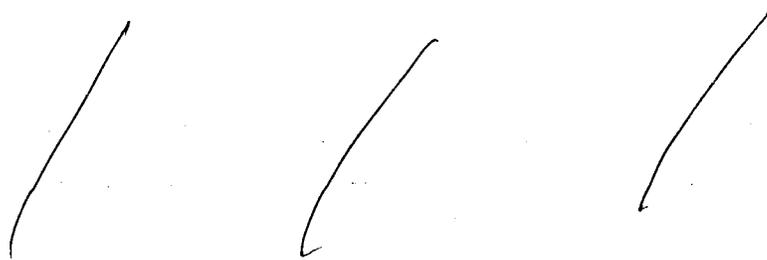
Renal and hepatic impairment:

- The population PK dataset of the phase 3 clinical trial IP631-018 consisted of patients with varying degrees of renal impairment: N = 129 with normal renal function (CrCL > 80 ml/min), N = 115 with mild renal impairment (CrCL: 50-80 ml/min), N = 30 with moderate renal impairment (CrCL: 30-50 ml/min), and N = 4 with severe renal impairment (CrCL < 30 ml/min). Data available did not suggest a clear impact of creatinine clearance on trosipium steady state concentrations.
- However, results from a special population study conducted earlier with the approved IR formulation suggested that severe renal impairment was associated with a 2.0-fold increase in mean C_{max} and a 4.5-fold increase in mean AUC

relative to healthy subjects. The approved dosing regimen in severe renal impairment is 20 mg QD at bedtime instead of 20 mg BID.

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- Moderate hepatic impairment (Child-Pugh 7-8) was associated with a 60% increase in mean C_{max}, a 15% decrease in AUC, and a 50% increase in renal clearance relative to healthy subjects administered with a single oral dose of 40 mg Sanctura 20 mg BID immediate release formulation. There is no information regarding the effect of severe hepatic impairment on the pharmacokinetics of trospium chloride. No dosing adjustment has been recommended in hepatic impairment when using the approved IR product.
- Most individuals within the population PK dataset had normal SGOT and SGPT levels (< 40 U/L). There was no correlation between hepatic enzyme levels and steady-state trospium concentrations.
- Because the overall exposure from once daily Sanctura XR 60 mg is lower relative to the approved 20 mg BID IR formulation, no dosage adjustment is recommended for the new formulation in presence of hepatic impairment.

Age:

- Age does not appear to influence trospium exposure from Sanctura XR. Observed trospium concentrations within the population PK dataset of the phase 3 clinical trial (IP631-018) suggest that the geriatric OAB patients (> 65 years) had concentrations similar to the younger OAB population; linear regression did not reveal significant correlation between age and plasma trospium (p = 0.58)
- While the overall frequency of adverse events was either similar or lower in the older patients of the phase 3 clinical trial compared to the younger patients, older patients exhibited a higher frequency of certain AEs including constipation, urinary tract infections and dyspepsia; Incidence rates are shown:
 - Constipation: < 65 years, 7.1%; ≥ 65 years, 14.0%
 - UTIs: < 65 years, 3.3%; ≥ 65 years, 10.5%
 - Dyspepsia: < 65 years, 1.1%; ≥ 65 years, 5.3%
- Numerically the age subgroup averages of efficacy endpoints (daily toilet voids and UUI episode frequency) were generally consistent with the overall sample values in the phase 3 trial 018.
- Efficacy assessments in the phase 3 clinical trial population (IP631-018) following once daily Sanctura XR 60 mg stratified by age group are shown;

Table 13: Efficacy outcomes stratified by age group; phase 3 clinical trial IP631-018

Primary efficacy endpoint: Average change in number of daily toilet voids (Mean ± SE)			
	Week	Age < 65 years (n = 182)	Age ≥ 65 years (N = 110)
Baseline		12.95 (0.2)	12.48 (0.22)
Change from Baseline	1	-1.9 (0.19)	-1.26 (0.21)
	4	-2.6 (0.19)	-2.19 (0.25)
	12	-2.99 (0.19)	-2.52 (0.23)
Co-primary endpoint: Average change in number of UUI episodes per day (Mean ± SE)			
	Week	Age < 65 years (n = 182)	Age ≥ 65 years (N = 110)
Baseline		4.12 (0.23)	4.09 (0.3)
Change from Baseline	1	-2.01 (0.17)	-1.61 (0.19)
	4	-2.45 (0.23)	-2.2 (0.23)
	12	-2.66 (0.22)	-2.17 (0.26)

- *No dosage adjustments are proposed based on age group.*
- Gender: PK data from 14 females and 8 males of the phase 1 definitive PK study IP631-020 suggested statistically significant differences in steady state tropsium PK across male and female subjects, with higher systemic exposure in females compared to males (AUC_t of 24241 pg.h/ml vs. 13024 pg.h/ml). The average C_{ss,max} value was also higher in females compared to males (2276 pg/ml vs. 1165 pg/ml). The inter-individual variability (%CV) in C_{max} was 86 % in females compared to 55 % in males, and % CV in AUC was 66 % in females vs. 38 % in males. The T_{1/2} values from male and female subjects with evaluable terminal elimination phase were numerically but not statistically different (40 h vs. 30 h in females vs. males).
- Overactive bladder predominantly exists in females. Majority of the phase 3 clinical trial patients in this NDA therefore were females (85 %). High steady-state tropsium concentrations (outliers > 7500 pg/ml) were observed entirely in females (such outliers constitute < 1.0 % of the total observed concentrations); however due to the markedly greater female enrollment (typical to OAB trials), the validity of this finding is not clear. Linear regression of the phase 3 concentration data suggested a statistically significant differences in steady state tropsium concentrations across genders (p = 0.04).
- Numerically the efficacy endpoint averages and ranges of change (in daily toilet voids and UUI frequency) across subgroups (male and female) are reportedly consistent with the overall treatment value. With respect to safety, the medical officer provided the following information: "The study reports did not specify any findings related to gender in either efficacy or safety. However, the study reports specifically states that with regard to safety, "The types of AE's described were generally consistent with events seen in other studies of antimuscarinic compounds used to treat OAB, and consistent with events in a population of patients with this age and **gender** demographic". In the phase 3 female patients who exhibited outlier concentrations of tropsium (n = 6), 'possible', 'moderate' AEs related to constipation, dry mouth, UTIs were observed, but did not suggest

any particular relationship or pattern with respect to observed high drug levels in these individuals;

- The observed higher exposure of trospium in females should not warrant a dosage adjustment, as clinical trials of Sanctura XR have been conducted in a majority (85%) of female patients (mimicking the clinical setting of OAB) and therefore safety and efficacy in this population has been adequately characterized.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Antacid Interaction:

- The effect of concomitant use of antacid on trospium exposure from Sanctura 60 mg XR was evaluated in study IP631-019; This was an open-label, single dose, randomized, 3-period crossover study in n = 12 healthy male and female volunteers (18-55 years) that also evaluated food-effect on PK.
- Trospium exposure from a single dose of Sanctura XR 60 mg administered in presence of antacid (20 ml \bar{m} Extra Strength liquid) was compared to the exposure observed following a single dose of Trospium 60 mg XR under fasted conditions.

Results:

- Study results were inconclusive with respect to the effect of antacid on trospium bioavailability from the XR formulation.
- Mean pharmacokinetic data was similar across treatment groups (with or without antacid). However, the 90 % CI surrounding the treatment mean ratios were outside the 80-125 % bounds.

Table 14: Summary of trospium pharmacokinetic parameters with or without antacid

Treatment	AUC _(0-∞) (pg* \bar{h} /mL)	AUC _(0-T_{last}) (pg* \bar{h} /mL)	AUC ₍₀₋₂₄₎ (pg* \bar{h} /mL)	C _{max} (pg/mL)	T _{max} ^a (h)	t _{1/2} (h)	HVD (h)
A (Fasted)	45500 (26400)	36400 (23100)	21700 (15800)	2640 (2240)	5.00	24.0 (9.97)	11.1 (16.1)
C (Fasted + Gaviscon)	39800 (25200)	39900 (25900)	21500 (17200)	2390 (2510)	5.25	27.5 (11.9)	14.9 (17.8)

Note: All values except those of T_{max} values reported as arithmetic mean (SD). SD = standard deviation; Gaviscon = Gaviscon® Extra Strength Liquid; ^aT_{max} expressed as median.

Table 15: Statistical Comparison of Trospium Pharmacokinetic Parameter Results for Fasted Groups with (Treatment A) and without Co-administration of Gaviscon® Extra Strength Liquid (Treatment C)

Parameter	N	Treatment	Geometric Least-Squares Mean	Pairwise comparisons		
				Pair	Ratio (%)	90% CI
AUC _(0-T_{max}) (pg* ^h /mL)	10	A	31890			
	12	C	33440	C/A	104.9	(77.7, 141.5)
AUC _(0-∞) (pg* ^h /mL)	7	A	41380			
	8	C	33090	C/A	80.0	(58.6, 109.0)
C _{max} (pg/mL)	10	A	1801			
	12	C	1643	C/A	91.2	(58.0, 143.5)

- Individual subject PK data suggested that 5 out of 11 subjects (ID # 9001, 9004, 9011, 9008, 9010) demonstrated a 2 to 4 fold increase or a decrease in trospium exposure (C_{max} and/or AUC) when dosed in presence of antacid.
- *Thus study results were found to be inconclusive to rule out an effect of antacid on trospium bioavailability.*

Table 16: Individual subject data from the antacid interaction study

Subj ID	Without antacid: A				With Antacid: C				Relative values: C/A		
	T _{max}	C _{max}	AUC _{last}		Subj ID	T _{max}	C _{max}	AUC _{last}		C _{max}	AUC _{last}
9001	5	432	19238		9001	5	983	21891.25		2.28	1.14
9002	6.5	1353	27304.5		9002	4	821	29636.95		0.61	1.09
9003	4	1139	18854.15		9003	4	1046	17376.5		0.92	0.92
9004	6	341	17002.8		9004	24	842	44906.3		2.47	2.64
9006	7	4821	86016		9006	7.5	3978	65151		0.83	0.76
9007	5.5	7444	54273.45		9007	6	8878	75156.5		1.19	1.38
9008	5	2843	32311.5		9008	5	983	22106.55		0.35	0.68
9009	5	1556	19864.9		9009	5	1066	17868.9		0.69	0.90
9010	6.5	1850	25721.15		9010	8	876	16658.2		0.47	0.65
9011	3	676	18604.7		9011	5	2783	45144		4.12	2.43
9012	5	4284	61356.1		9012	6	5250	95016.75		1.23	1.55

Alcohol Interaction: In vitro testing

- In vitro release of trospium was assessed in presence of various strengths of alcohol (0 %, 10 %, 15 %, 20 % and 40%).
- The dissolution medium employed was simulated gastric medium (750mL of 0.1N HCl, pH 1.1 for 2 hours) adjusted to various alcohol concentrations. After 2 hours the medium was then adjusted (as in the controls) to pH 7.5 with 200mL of 0.1N NaOH in 200mM phosphate buffer.

Results: All data presented are for Lot 0501442 which was a clinical and registration batch of the drug product.

- 10 %, 15 %, 20 % alcohol strengths did not have a significant impact on trospium release from the modified release formulation; approximately 95 % release occurred by 12 h similar to that seen in the control (no alcohol) group.
- On the other hand, with 30 % alcohol strength, ~ 95 % release occurred by 8 h.
- At the highest evaluated concentration (40 % alcohol), ~ 95 % of drug was released within the first 2 hours.

Reviewer's comments: The potential for dose dumping from Sanctura XR in presence of 40 % alcohol is evident from these in vitro study results; this information should be communicated in the product label. Sanctura XR should not be taken in presence of alcohol.

**APPEARS THIS WAY
ON ORIGINAL**

LIMS ID	Hours:										
	0	1	2	2.5	3	4	8	12	16	20	
3446	no ethanol	0	8	21	51	67	73	88	95	98	100
7341	10% ethanol	0	5	14	53	61	89	90	98	99	101
7433	15% ethanol	0	5	15	61	63	85	87	95	101	103
7434	20% ethanol	0	5	12	56	60	83	81	90	95	98
7435	30% ethanol	0	14	55	78	79	84	94	99	101	103
7342	40% ethanol	0	75	94	81	92	94	99	100	101	102

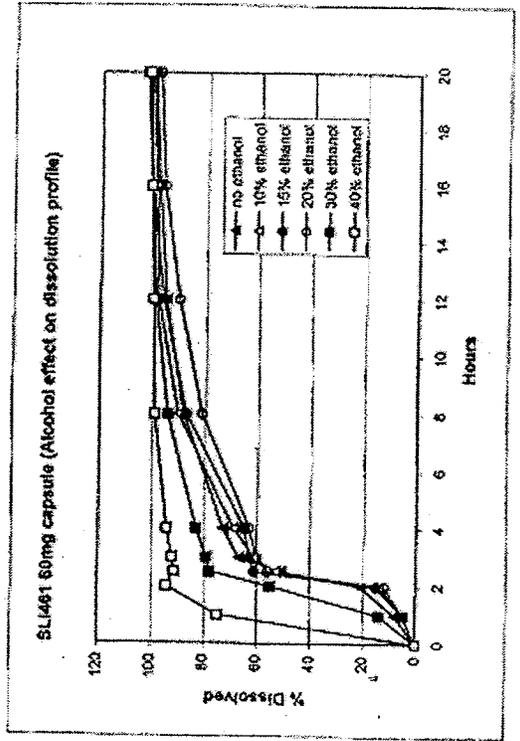
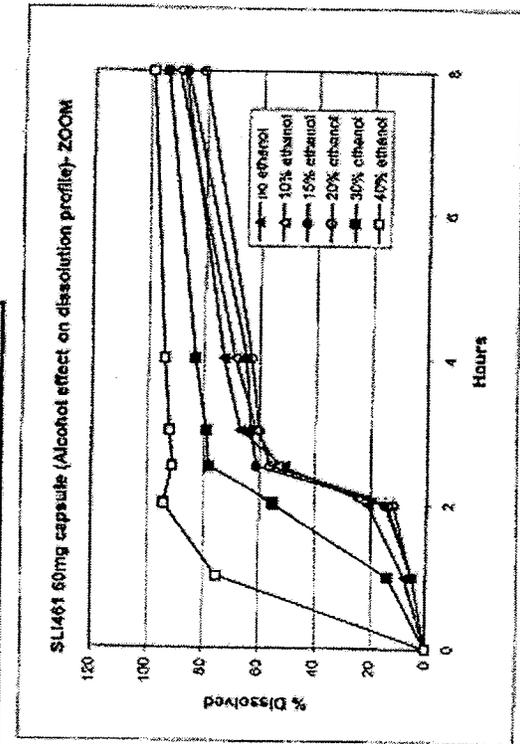


Figure 7: Results of the in vitro alcohol interaction study

2.4.2 Drug-drug interaction potential

- No drug-drug interaction studies have been conducted in support of Sanctura XR (NDA 22-057). The drug metabolic pathway and drug-drug interaction potential of trospium chloride was reviewed during the review of NDA 21-595 for the immediate release product.
- Information contained within the CPB review (reviewed by Dr. Leslie Kenna, 05/26/2004) of the original NDA suggests that trospium elimination occurs via hydrolysis by the action of esterase, followed by glucuronide conjugation of benzylic acid to form the inactive major metabolite Azoniaspironortropanol.
- Preclinical data did not suggest involvement of cytochrome P450 enzymes in trospium metabolism.
- In vitro studies did not suggest clinically relevant inhibitory affect of trospium on various CYP450 enzymes including 1A2, 2C19, 2D6, 2E1, 3A4, 2A6, and 2C9. Therefore, the likelihood of drug-drug interactions is low. No in vivo drug-drug interaction studies related to CYP450 involvement have been conducted.
- Trospium undergoes active renal secretion and therefore other renally eliminated drugs may interfere with its clearance.
- A study conducted to investigate the effect of digoxin and trospium did not demonstrate significant changes in the exposure of either drug.

2.5 General Biopharmaceutics:

2.5.1 Is the proposed commercial (TBM) formulation similar to the clinical trial formulation of Sanctura XR?

- *The clinical and the to-be-marketed formulations are identical based on the information submitted in Module 2/Drug Product/Pharmaceutical Development. The CMC PAL Dr. Donna Christner concurs with this conclusion as well.*
- The sponsor reported few changes that occurred during drug development; changes to the formulation are summarized in the table below:

Table 17: Tabulated summary of formulations of Sanctura XR in various phases of drug development

Tabulated Summary of Formulations of Sanctura XR in Various Phases of Drug Development

Study Phase	Study ID	Lot #	Formulation	Drug Substance Supplier	Site of Mfr.	Production Scale	% drug load of the	Other formulation or mfr related changes
1	IP631-011	B04017*				Lab Scale		
2	IP631-016	B04037*				Lab Scale		
1	IP631-019	0501444D				Pilot Scale		
1	IP631-020	0501439D 0501444D				Pilot Scale		
3	IP631-018	0501442D				Pilot Scale		
3	IP631-022	0501444D				Pilot Scale		

* Lot B04017 is the same as Lot B04037

to that observed when dosing occurred 30 minutes after the start of a high-fat morning meal.

Results:

- Dosing in presence of food (50 % calories from fat) did not result in dose dumping from this MR formulation.
- T_{max} and T_{1/2} remained unchanged under fed conditions.
- Food decreased the rate and extent of bioavailability, with average C_{max} and AUC_{last} values that were 33 % and 60 % compared to the exposure when dosed under fasting conditions.
- The 90 % CI surrounding the fed/fasted treatment ratio was outside the 80-125 % range that was necessary to show absence of food-effect.
- *These results suggest significant food effect; Trospium XR should be dosed under fasted conditions.*

Table 18: Summary of trospium pharmacokinetic parameters (Fed vs. Fasted)

Treatment	AUC _(0-∞) (pg*h/mL)	AUC _(0-T_{last}) (pg*h/mL)	AUC ₍₀₋₂₄₎ (pg*h/mL)	C _{max} (pg/mL)	T _{max} ^a (h)	t _{1/2} (h)	HVD (h)
A (Fasted)	45500 (26400)	36400 (23100)	21700 (15800)	2640 (2240)	5.00	24.0 (9.97)	11.1 (16.1)
B (Fed)	29400 (9220)	22000 (7700)	10400 (5550)	877 (722)	5.25	26.8 (8.22)	26.3 (19.9)

Note: All values except those of T_{max} values reported as arithmetic mean (SD). SD = standard deviation;
^a T_{max} expressed as median.

Table 19: Statistical comparison of trospium pharmacokinetic parameter results for fasted (A) and fed (B) groups:

Parameter	N	Treatment	Geometric Least-Squares Mean	Pairwise comparisons		
				Pair	Ratio (%)	90% CI
AUC _(0-T_{last}) (pg*h/mL)	10	A	31890			
	12	B	20780	B/A	65.2	(48.3, 88.0)
AUC _(0-∞) (pg*h/mL)	7	A	41380			
	5	B	34610	B/A	83.6	(55.3, 126.6)
C _{max} (pg/mL)	10	A	1801			
	12	B	723.7	B/A	40.2	(25.5, 63.2)

2.5.3 Dissolution

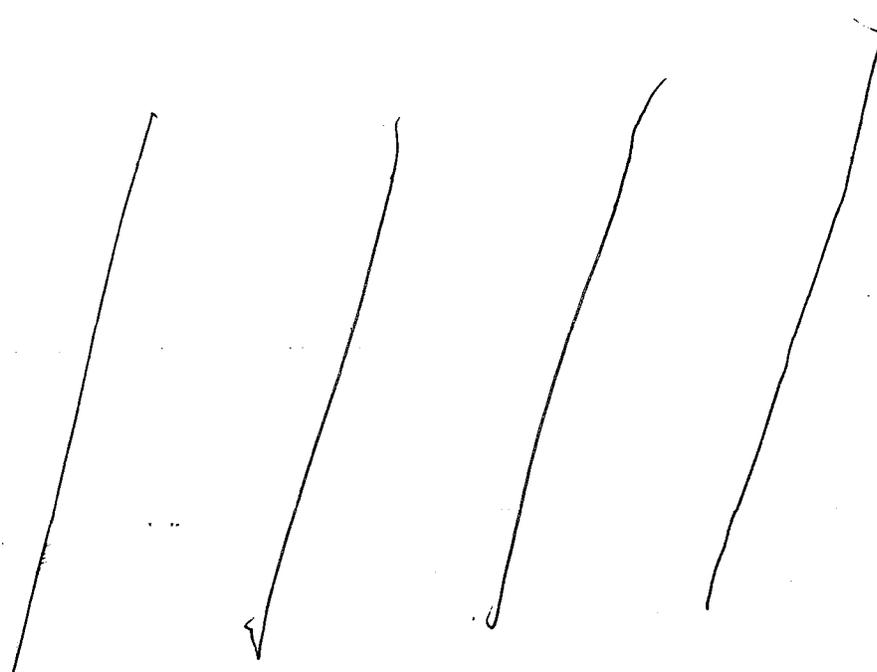
Sanctura XRTM trospium chloride capsules are

Release specifications have been proposed for components as well as for the final capsule formulation to ensure adequate product performance. In addition, Indevus is

proposing to discontinue release testing of the _____
for the commercial batches, as full release is performed for the final _____
_____ products. Indevus is intending to only sample at the
specification pull times for future commercial batches as listed below:

Proposed dissolution methodology and commercial Release Specifications:





Final formulation — Capsules: — 50mg): Since the capsules are extended release finished products, the specification pull times were selected to define the early, middle and late stages of the release.

Table 22: Final dissolution specifications for the — formulation

Dissolution ^{a,b}	USP Apparatus II Media: 0.1N HCl, pH 1.1; 750mL; 50rpm for 2 hours. Media adjustment to pH 7.5 with 200mL of 0.1N NaOH in 200mM phosphate buffer after 2 hours. Analysis method: HPLC	Time (hours)	% Dissolved
		2.0	—
		3.0	—
		16.0	—

^aAcceptance criteria follow current USP dissolution chapter including level L₁ and L₃ testing, where applicable.

^bReport dissolution results at 2, 3, and 16 hours.

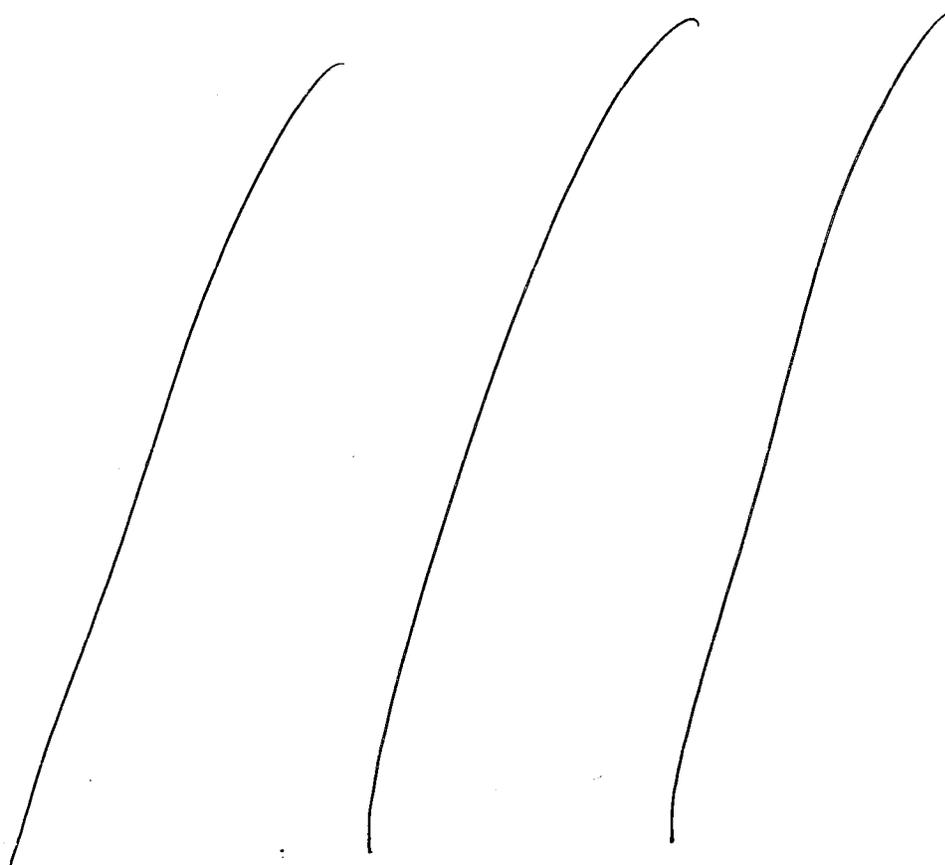
Reviewer comments:

- The proposed dissolution methodology and changes to the release specifications and the above issue were discussed in-detail with the CMC reviewer Dr. Gene Holbert and CMC PAL Dr. Donna Christner.
- Sponsor's proposal not to conduct release testing of the — and the — appears reasonable, as subsequent testing of the — and the final encapsulated product will assure adequate in vitro release performance.

- Extract stability: Results indicate that Trospium is stable in processed human plasma for at least 65.8 hours at room temperature. The accuracy for Trospium at 65.8 hours was $\leq 12.3\%$.
- Frozen Storage Stability: Long-term frozen storage stability at -20°C was examined at 6 days concurrent with Run 8. The results indicate that Trospium is stable in human plasma for at least 6 days at -20°C , with an accuracy of $< 12.4\%$.

3 Labeling

The broad clinical pharmacology labeling recommendations to the Sanctura XR label are summarized below:



4 Appendix

4.1 OCP Filing Review

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	22-103	Brand Name	Sanctura XR	
OCP Division	DCP3	Generic Name	Trospium chloride	
Medical Division	DRUP	Drug Class	Antimuscarinic	
OCP Reviewer	Sandhya Apparaju	Indication(s)	Overcrtive Bladder (OAB)	
OCP Team Leader	Myong Jin Kim (Acting TL)	Dosage Form	Extended release capsules	
		Dosing Regimen	Once daily in the AM; fasted	
Date of Submission	10/12/2006	Route of Administration	Oral	
Estimated Due Date of OCP Review	06/12/2007	Sponsor	Indevus Pharmaceuticals, Inc	
PDUFA Due Date	08/13/2007	Priority Classification	Standard	
Division Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			Included in Module 5
HPK Summary	X			Included in M2 (Clinical Overview)
Labeling	X			New SPL format; Also available as an annotated version with links to relevant sections of the NDAs (22103 and 21595).
Reference Bioanalytical and Analytical Methods	X			Analytical reports from _____ have been submitted.
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) - Healthy Volunteers-				
single dose:	X	1		IP631-019: Food effect and antacid interaction study in healthy adults

multiple dose:	X	2		IP631-011 (Pilot bioavailability study). IP631-020 (XR vs. IR).
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		IP631-019; Antacid interaction
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	1		IP631-020; Steady state PK in Geriatric subjects following 30 mg XR capsules
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				

Data sparse:	X	2		<p>IP631-016; 2-week, Phase 2 study of 60 mg XR vs. placebo, given AM or PM in OAB patients; Study included sparse sampling for PK. Correlations between drug concentrations and few efficacy, as well as safety endpoints was attempted.</p> <p>IP631-018: Phase 3 clinical trial; <u>Sparse sampling data and analysis report from this study will be submitted as an amendment to the NDA (4 months into the review cycle)</u> as indicated by the sponsor during the pre-NDA meeting; see relevant pre-NDA minutes for IND 71305 for discussion related to this arrangement.</p>
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability - solution as reference:				
alternate formulation as reference:	X	1		IP631-020 (the new XR formulation is compared against the currently approved IR formulation of Trospium)
Bioequivalence studies - traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		IP631-019
Dissolution:	X	1		Dissolution in presence of two strengths of alcohol
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics	X	1		IP631-016: The effect of diurnal effect on PK (AM vs. PM dosing) was evaluated using population PK assessment in this phase 2 study.
Pediatric development plan				Waiver has been requested
Literature References	X			

Total Number of Studies	<input checked="" type="checkbox"/>	7		IP631-009, 011, 016, 018, 019, 020 and alcohol release data; Above studies include pilot PK, Phase 1 single dose and multiple dose PK, Phase 2 and Phase 3 Population PK assessments, Food interaction, Geriatric PK, diurnal variability in PK, antacid interaction and in vitro alcohol interaction information.
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Filability and QBR comments

- The clinical trial vs. to-be-marketed formulations of Sanctura XR are identical.

The following comments/information requests will be sent to the sponsor in the 74-day letter:

- Submit a tabulated summary describing the various formulations of Sanctura XR employed in the various phases of drug development. Such a table should include the following columns:

Study Phase (pilot, I, II or III)	Study ID	Lot #	Formulation (qualitative and quantitative description)	Drug substance supplier	Site of Manufacture	Production scale	% drug	Any other formulation or manufacturing related changes
							— — — —	

- As discussed during the pre-NDA meeting (See minutes dated October 12, 2006), we remind you to submit the population PK data and study report from the Phase 3 clinical trial IP631-018, at the latest by Month 4 into the review cycle.
- Submit the following datasets that could not be located in the NDA in SAS transport file format:
PK parameters for individual subjects of IP631-019 and IP631-020.
Drug concentrations for individual subjects of Phase 2 clinical trial IP631-016.
- _____ will be a review issue.
- Dosing in presence of alcohol will be a review issue.

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Above comments will be sent to firm in the 74-day letter.
QBR questions (key issues to be considered)		Single dose and multiple dose PK. Food-effect on bioavailability Antacid interaction Geriatric PK Diurnal variability Alcohol interaction Dosing in special populations

Other comments or information not included above	
Primary reviewer Signature and Date	Sandhya Apparaju; 12/04/2006
Secondary reviewer Signature and Date	

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 22-103

Compound: Trospium Chloride Extended Release Capsules (Sanctura XR)

Sponsor: Indevus Pharmaceuticals, Inc.

Date: 11/28/2006

Reviewer: Sandhya Apparaju, Ph.D.

Background:

Trospium chloride, is an anticholinergic drug, currently approved for marketing as an immediate release formulation for twice-daily administration (Sanctura; NDA 21-595), for treatment of the signs and symptoms of OAB. The development program for NDA 22-103 was aimed at designing a more convenient once-daily formulation of trospium chloride with similar efficacy characteristics as the BID product and an improved safety profile. To this end, the sponsor has developed and evaluated an extended release formulation of Trospium chloride (Sanctura XR 60 mg) comprising

NDA 22-103 for Sanctura XR was submitted on October 12, 2006 and includes CMC, clinical pharmacology, safety, efficacy information for the extended release formulation.

List of studies submitted in the NDA that contain clinical pharmacology relevant information:

IP631-009: A pilot, comparative, randomized, 6-way crossover bioavailability study of Indevus trospium chloride new formulations and Spasmo-lyt 20 mg trospium chloride tablets in healthy adult female volunteers under fasting conditions. While the results of this study in conjunction with PK simulation and modeling were stated to have been useful in further refinement of Trospium chloride formulations for use in subsequent studies, this study in itself did not include the final formulation.

IP631-011: This was a Phase I, open-label, randomized, 5-way crossover pilot study in healthy volunteers (N = 25) to determine the pharmacokinetics of 4 once-daily formulations: A) capsules, B) capsules, C) capsules, D) 60 mg Capsules and E) Trospium chloride 20 mg tablets (given BID). This study included the final formulation.

IP631-019: A Phase I, single-center, single-dose, open label, randomized, 3-period, 3-arm crossover, bioavailability design to assess the pharmacokinetic effect of food or co-administration of an antacid on Sanctura XR 60 mg. N = 12 healthy subjects.

IP631-020: This was a Phase I, multiple dose, randomized, open-label, 2-period, 2-arm crossover bioavailability study in healthy adult subjects to characterize the steady state PK and compare the relative bioavailability of trospium chloride and its major metabolite, azaniaspironortropanol from Sanctura XR 60 mg capsules QD vs. trospium chloride 20 mg tablets BID following 10 days of dosing on each regimen. The study also evaluated the steady state PK of Sanctura XR 30 mg capsules following 10 days of dosing in geriatric subjects. Subjects included N = 24 healthy adult volunteers (18-55 years and 11 Geriatric subjects (65-80 years).

IP631-016: A Phase II, multi-center, parallel, randomized, double-blind, placebo-controlled, 2-week treatment trial in patients with OAB to compare two different dosing regimens (morning or evening dosing)

of Sanctura XR 60 mg QD capsules and placebo. N = 49 on placebo and N = 50 on Sanctura XR AM dose and N = 49 on Sanctura XR PM dose. A population PK report from this study is also available.

IP631-018: A Phase III, multi-center, parallel, randomized, double-blind, placebo-controlled, 12-week treatment trial in patients with OAB, followed by an optional 9-month open-label treatment phase. Treatments evaluated were an Oral dose of Sanctura XR 60 mg QD in the morning and matching placebo. N = 600 patients; (age: 18 years and older); A population PK report based on this study as well as studies IP631-016 (Phase II) and IP631-020 (Phase I), is planned for the 120 day safety update to this NDA.

Alcohol Interaction: An in vitro study was conducted on the effect of 10% and 40% ethanol concentrations on the dissolution of Sanctura XR 60 mg capsules. Sponsor concludes that 10 % alcohol had no effect on the drug release profile of Trospium chloride XR 60 mg capsules (F2 value 69). Exposure to extreme alcohol levels of 40% ethanol resulted in 90% dissolution within 2 hours in the 0.1N HCl medium.

QT Prolongation potential: Thorough QT studies conducted for NDA 21595 (IR 20 mg BID Trospium) did not show QT interval prolongation at therapeutic and supra-therapeutic doses.

Drug metabolism and drug interaction potential: Trospium is metabolized by ester hydrolysis and excreted by the kidneys through a combination of tubular secretion and glomerular filtration. No clinically relevant metabolic drug-drug interactions are anticipated with SANCTURA XR (reviewed under previous NDA 21595).

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. In a drug-interaction study with digoxin, concomitant use of the drugs did not alter the PK of either drug.

Special populations:

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, 4.5-fold and 2-fold increases in mean AUC(0-∞) and C_{max}, respectively, were detected in patients with severe renal impairment (CL_{cr} < 30 mL/min), compared with healthy subjects, along with the appearance of an additional elimination phase with a long half-life (~33 hours vs. 18 hours). The approved product labeling for the IR formulation recommends a less frequent dose of 20 mg once daily at bed time in patients with severe renal impairment.

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-to-severe (Child-Pugh score 7-12) hepatic impairment, given 40 mg of immediate-release trospium chloride, C_{max} increased 12% and 63% respectively, compared to healthy subjects. Mean AUC changes were similar. The increases were not statistically significant and so the clinical significance of these findings is unknown. Caution is advised, however, when administering SANCTURA XR to patients with severe hepatic impairment. No dosage adjustment is recommended for the currently approved Trospium IR formulation.

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.

Sponsor's own conclusions state that no overall differences in safety or effectiveness were observed between these and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The steady-state pharmacokinetic study of 30 mg doses of SANCTURA XR were evaluated in Study IP631-020 in geriatric subjects (mean age 67.5 years).

No dosage adjustment for the XR formulation is proposed in geriatric patients. This will be a review issue.

The currently approved IR product labeling recommends a less frequent dose of 20 mg once daily in geriatric patients based only on tolerability; no differences in PK were observed for the IR formulation in the geriatric vs. young populations.

Pending submissions: The population pharmacokinetic outcomes from study IP631-018 (Phase 3 clinical trial) will be reported in a separate amendment to the NDA. This was proposed by the sponsor during the pre-NDA meeting and the agency provided the following recommendation at that time: (See IND 71305 pre-NDA meeting minutes (see sponsor's question and CP answer below)):

Clinical Pharmacology Response: Yes, it is acceptable to submit the population pharmacokinetic (PK) data analysis at 4 months into the review cycle. However, due to the logistical considerations involved in a review process (e.g., the need for a pharmacometric consult, etc.), any data that is critical for final labeling should ideally be submitted at the time of initial NDA submission to allow a thorough and timely review.

Clinical vs. TBM formulations: The clinical and the to-be-marketed formulations are identical based on the information submitted in Module 2/Drug Product/Pharmaceutical Development. The CMC PAL Dr. Donna Christner concurs with this conclusion as well.

The sponsor reports few changes that occurred during drug development:

Drug substance supplier changed from _____ to _____ however most of the phase 1 and all phase 3 trials were conducted using the final supplier _____

The manufacturing of _____ was changed: briefly _____

_____ the overall amount of drug remained the same; Based on the release data below (Figure 1 and Table 2), this change did not alter the release profile (Similarity factor F2 values reported as between 61 and 70); moreover it appears that some of the batches of this changed formulation were evaluated in the phase 1 and phase 3 clinical trials (IP631-019, 020, 018, 022); Following the phase 1 and 2 studies, the manufacturing batch size was changed from lab scale to pilot scale.

The manufacturing of the drug product was transferred from the _____ to the selected commercial manufacturing site, _____

Of the changes discussed above, the changes in the drug supplier and in the manufacture of the formulation, and the change from lab scale to pilot scale production did not alter the drug release profile as shown in the data below:

Table 1: Clinical Drug Lots, Drug Substance Supplier and Scale

Study	DP Lot #	DS Supplier	Manufacturing
IP631-011	B04017	—	Lab scale
IP631-016	B04037+	—	Lab scale
IP631-019	0501444D	—	Pilot scale
IP631-020	0501439D 0501444D	—	Pilot scale
IP631-018*	0501442D	—	Pilot scale
IP631-022*	0501444D	—	Pilot scale

*Phase III Studies

+This is the same lot as B04017

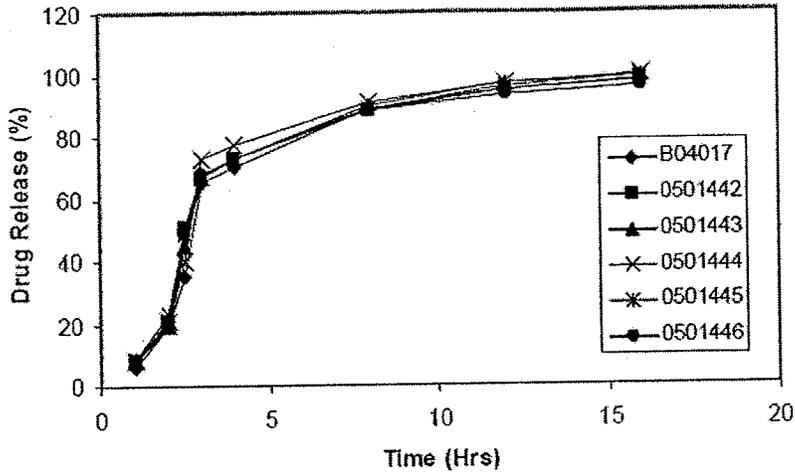


Figure 1: Dissolution Profiles of Lots Used in Clinical Trials

The sponsor confirmed that the formulations are identical (clinical vs. TBM) during a teleconference on 12/01/2006:

RE: NDA 22-103 Sanctura XR™ (trospium chloride extended release) Capsules
Response to FDA request for information

This letter is provided as an amendment to NDA 22-103 and is in response to a specific inquiry from the agency, presented in a telephone conversation held on 1 December 2006. The NDA reviewing Division asked if the change made in the _____ for the drug product Sanctura XR, was made prior to the manufacture of the clinical trial lots of capsules and if these clinical trial lots were of the same final formulation as that filed in the NDA and intended for commercial manufacture.

The sponsor confirms that the _____ formulation was used in the Phase 3 clinical trials (lots 050144D, 0501442D and 0501439D) and that this will be the same formulation used in the commercial Sanctura XR capsules.

Recommendation:

The Office of Clinical Pharmacology /Division of Clinical Pharmacology III find that the Human Pharmacokinetics and Bioavailability section for NDA 22-103 is filable.

 Sandhya Apparaju, Ph.D. Primary Reviewer

 Date

 Myong Jin Kim, Ph.D., Acting Team Leader

 Date

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sandhya Apparaju
7/2/2007 10:03:41 AM
BIOPHARMACEUTICS

Myong-Jin Kim
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