

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-595

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

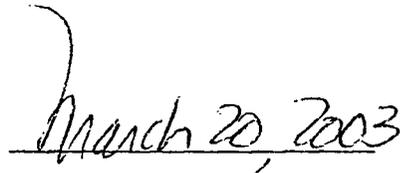
13. PATENT INFORMATION ON ANY PATENT THAT CLAIMS THE DRUG

Indevus is not aware of any patent that claims trospium chloride (as a drug substance or as an ingredient of a drug product) or claims the use of trospium chloride in the treatment of overactive bladder. Indevus, however, reserves the right to submit supplementary patent information should patent(s) relevant to the NDA come to light.

Submitted by:



Mark Butler
Executive Vice President
Chief Administrative Officer and General Counsel
Indevus Pharmaceuticals, Inc.



Date

EXCLUSIVITY SUMMARY for NDA # 21-595 SUPPL #

Trade Name Sanctura Generic Name trospium chloride

Applicant Name Indevus Pharmaceuticals HFD- 580

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 !
 IND # _____ YES /___/ ! NO /___/ Explain:
 !
 !
 !

Investigation #2 !
 !
 IND # _____ YES /___/ ! NO /___/ Explain:
 !
 !
 !
 !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 !
 YES /___/ Explain _____ ! NO /___/ Explain _____
 !
 _____ ! _____
 !
 _____ ! _____
 !

Investigation #2 !
 !
 YES /___/ Explain _____ ! NO /___/ Explain _____
 !
 _____ ! _____
 !
 _____ ! _____
 !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature of Preparer
Title:

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD-580/Division File
HFD-580/Dale Cutright/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Dale Cutright
5/27/04 02:29:34 PM

Jennifer L. Mercier
5/27/04 02:52:48 PM
For Daniel Shames, M.D. - Director

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

VA/BLA #: 21-595 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: April 29, 2003 Action Date: May 28, 2004

HFD-580 Trade and generic names/dosage form: trospium chloride 20 mg tablets

Applicant: Indevus Pharmaceuticals, Inc. Therapeutic Class: S1

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Overactive Bladder

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. <5 Years Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

udies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 5-15 years Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): December, 2005

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Dale Cutright
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

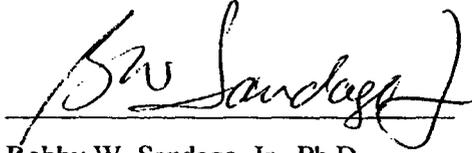
/s/

Dale Cutright

5/25/04 12:49:29 PM

16. DEBARMENT CERTIFICATION

Indevus Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Bobby W. Sandage, Jr., Ph.D.
Executive Vice President, Research and Development
Indevus Pharmaceuticals, Inc.

4-22-03

Date

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Indevus Pharmaceuticals, Inc. 99 Hayden Avenue, Suite 200 Lexington, MA 02421	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-595
2. TELEPHONE NUMBER (Include Area Code) (781) 402-3406	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: NDA 21-595 (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Trospium Chloride	6. USER FEE I.D. NUMBER 4529

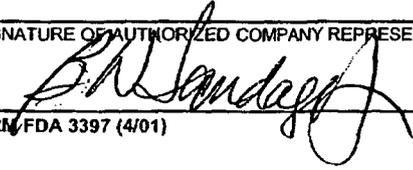
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE EVP, Research & Development	DATE 4/23/03
---	--------------------------------------	-----------------

NDA 21-595
Sanctura

Application Integrity Policy

Not applicable for this application.

**APPEARS THIS WAY
ON ORIGINAL**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-595		
Drug: Sanctura™ (trospium chloride) 20 mg Tablets		Applicant: Indevus Pharmaceuticals, Inc.
RPM: Dale Cutright	HFD- 580	Phone # 301-827-7508
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	Reference Listed Drug (NDA #, Drug name): n/a	
❖ Application Classifications:		
• Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)	1	
• Other (e.g., orphan, OTC)	n/a	
❖ User Fee Goal Dates 5/28/04 (w/3 mo ext)	x	
❖ Special programs (indicate all that apply)		
	<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	
❖ User Fee Information		
• User Fee #4529 Pd 4/11/03	<input checked="" type="checkbox"/> Paid	
• User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health n/a <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
• User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) n/a <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)	n/a	
• OC clearance for approval	n/a	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
	<input checked="" type="checkbox"/> Verified	
❖ Patent		
• Information: Verify that patent information was submitted	<input checked="" type="checkbox"/> Verified	
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) n/a <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	<input type="checkbox"/> Verified n/a	
❖ Exclusivity Summary (approvals only)		
	x	

Administrative Reviews (Project Manager, ADRA) 7/10/03	x
❖ Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	n/a
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling) 5/1/04	x
• Most recent applicant-proposed labeling 3/23/04	x
• Original applicant-proposed labeling 1/30/04	x
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings) ODS 2/13/04; 12/8/03; DDMAC 2/10/04; 10/10/03	x
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	n/a
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	n/a
• Applicant proposed	x
• Reviews	x
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	x
• Documentation of discussions and/or agreements relating to post-marketing commitments	x
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	x
❖ Memoranda and Telecons	x
❖ Minutes of Meetings	
• EOP2 meeting (indicate date) 5/22/00	x
• Pre-NDA meeting (indicate date) 12/9/02	x
• Pre-Approval Safety Conference (indicate date; approvals only) 5/4/04	x
• Other	n/a
❖ Advisory Committee Meeting	
• Date of Meeting	n/a
• 48-hour alert	n/a
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	n/a

Initial and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	x
❖ Clinical review(s) (<i>indicate date for each review</i>)	x
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	n/a
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	x
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	x
❖ Statistical review(s) (<i>indicate date for each review</i>) 6/13/03	x
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>) 6/30/03, 7/1/03	x
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies 12/15/03; 12/8/03; 12/2/03; 11/18/03	x
• Bioequivalence studies	n/a
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>) 7/8/03	x
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	See Review
• Review & FONSI (<i>indicate date of review</i>)	See Review
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	See Review
Micro (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	n/a
❖ Facilities inspection (provide EER report)	Date completed: (x) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (x) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews 6/24/03; 2/12/04	x
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) 2/12/04	x
❖ CAC/ECAC report	n/a

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA # 21-595 Supplement # _____ SE1 SE2 SE3 SE4 SE5 SE6 SE7
SE8

Trade Name: Sanctura
Generic Name: trospium chloride
Strengths: 20 mg

Applicant: Indevus Pharmaceuticals, Inc.

Date of Application: 4-28-03
Date of Receipt: 4-29-03
Date of Filing Meeting: 6-12-03
Filing Date: 6-27-03

Indication(s) requested: Overactive Bladder

Type of Application: Original (b)(1) NDA X Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S X P _____
Resubmission after a withdrawal N/A or refuse to file N/A
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A YES NO

Is the application affected by the application integrity policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A YES NO

User Fee Status: Paid Ck# 29540 Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee ID # 4529
Clinical data? YES X NO _____, Referenced to NDA # _____

Date clock started after UN: _____

User Fee Goal Date: 2/27/04

Action Goal Date (optional): 2/27/04

- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES NO

- Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information included with authorized signature? YES NO
- Exclusivity requested? YES, 5 years NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix _____." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure information included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)
- Has the applicant submitted pediatric data and/or deferral request and/or waiver request for all ages and indications? NEED TO REVISE OR DELETE THIS STATEMENT
YES NO

Chemistry

- | | | |
|---|------------|-----|
| • Did applicant request categorical exclusion for environmental assessment? | <u>YES</u> | NO |
| If no, did applicant submit a complete environmental assessment? | YES | NO |
| If EA submitted, consulted to Nancy Sager (HFD-357)? | YES | NO |
| • Establishment Evaluation Request (EER) submitted to DMPQ? | <u>YES</u> | NO |
| • If parenteral product, consulted to Microbiology Team (HFD-805)? | <u>N/A</u> | YES |
| | | NO |

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

	YES	NO
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- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

	YES	NO
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- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

	YES	NO
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- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
 - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

	YES	NO
--	-----	----
 - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

	YES	NO
--	-----	----
 - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

	N/A	YES	NO
--	-----	-----	----
 - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

	N/A	YES	NO
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- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
 - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

	YES	NO
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 - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

	YES	NO
--	-----	----
 - EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

	YES, IND # _____	NO
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OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-595
Sanctura

Press Office Information

Not applicable for this application.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
ODE 3
Division of Reproductive and Urologic Drug Products**

Date: May 27, 2004

From: Mark S. Hirsch, M.D., Medical Team Leader, HFD-580

To: Dan A. Shames, M.D., Division Director, HFD-580

Subject: NDA 21-595
Sanctura (trospium chloride) 20mg Tablets for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency.

1. Executive summary

The purpose of this memo is to provide the Division Director with my recommendation regarding regulatory action on this NDA. At this time, I recommend that Sanctura should be **approved** for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency. The sponsor has demonstrated through adequate and well-controlled trials that the benefits of Sanctura outweigh the risks in the treatment of overactive bladder. There are no outstanding issues.

2. Clinical background

Overactive bladder (OAB) is a common disorder affecting millions of Americans. It is most prevalent among middle-aged and geriatric females, but it also exists in men. The well-described OAB symptom complex includes urinary frequency, urinary urgency, and in some patients, urge urinary incontinence. OAB is related to the presence of involuntary contractions of the detrusor (bladder wall) smooth muscle that results in a decrease in the ability to store urine. Usually, there is no clear direct etiology for this dysfunction. In some patients, involuntary detrusor contractions are directly related to a known neurological condition and in these patients, the condition is referred to as detrusor hyperreflexia.

In OAB, therapy is generally directed at the bladder wall smooth muscle, with the objective of relaxing the bladder so that it is capable of holding more urine for a longer period of time prior to experiencing an involuntary contraction. This sort of therapy is intended to relieve symptoms of urgency (the urgent need to void), lessen urinary frequency (or voluntary voids), and to reduce incontinence episodes.

The mainstay of treatment for OAB has been and continues to be anticholinergic medications. These include tolterodine (Detrol and Detrol LA) and oxybutynin (Ditropan, Ditropan XL and Oxytrol). Older anticholinergics used for this purpose also include hyocymine (Levsin) and propantheline (Pro-Banthine). Unfortunately, treatment of OAB with anticholinergics has been limited by well-recognized side effects including dry mouth, constipation, urinary retention, dry skin, vision disturbances, tachycardia, and changes in mental status.

Recent efforts in OAB have included an attempt to develop more bladder wall-selective anti-muscurinic (anticholinergic) agents and to develop formulations that are more convenient and may lessen side effects through reduction in exposure to the parent drug or the metabolites.

In this NDA, the sponsor has proposed trospium chloride for the treatment of OAB. Trospium chloride is a fairly old compound and has been approved in Europe for treatment of urinary incontinence for at least a decade. The sponsor has developed a novel formulation of the drug substance that they believe is effective in relieving OAB symptoms with an acceptable tolerability profile. The potential benefits of this medication over currently available treatments include the fact that a large part of trospium is eliminated through ester hydrolysis and active renal secretion, not through hepatic cytochrome P450 metabolism. This property may limit the potential for pharmacokinetic drug interactions. Further, trospium is a charged molecule and sponsor believes that this property makes penetration into the central nervous system (CNS) poor, providing a potential for fewer CNS-related side effects, such as delirium and sedation.

Reviewer's comments:

- 1. Drugs that are eliminated by active secretion may (theoretically) interact with other drugs eliminated by active secretion. While this is not a cytochrome P450-related metabolic interaction, it must still be considered when administering Sanctura.**
- 2. Despite the theoretical potential for Sanctura to reduce CNS-related adverse reactions (and acknowledging the overall low rates of reported CNS adverse events in this NDA), the evidence is not yet sufficient to conclude that Sanctura is better than other anticholinergic medications or equivalent to placebo for CNS-related adverse reactions.**
- 3. Nevertheless, the reviewer believes that Sanctura offers another option in OAB treatment.**

In this application, NDA 21-595, the sponsor submitted two, U.S., randomized, placebo-controlled, double-blinded, 3-month treatment period, Phase 3, clinical efficacy and safety trials and one U.S. 9-month open-label extension trial to support the OAB indication. In addition, the sponsor submitted study reports for several older, non-U.S. studies, including a randomized, placebo-controlled, double-blinded study using urodynamic (pharmacodynamic) assessments as the measure of efficacy, two shorter-term (3 week) randomized studies, and results from a 52-week active-controlled trial. This medical team leader's memorandum focuses on the U.S. trial results and makes some reference to the non-U.S. studies. The more recent, more well-documented, and prospective U.S. studies comprise the summary basis for approval.

3. Design of the controlled studies submitted in support of the application

In support of the efficacy and safety of Sanctura for the OAB indication, the sponsor submitted the results from:

1. Studies -03 and -05: two, 12-week, U.S., Phase 3, randomized, placebo-controlled trials;
2. Studies -14 and -15: two, 3-week, randomized, placebo-controlled European studies including a "pharmacodynamics" (urodynamics) component in Study -14;
3. Study -04: a 52-week, randomized, active-controlled European study; and
4. A nine-month, open-label extension to the first U.S. pivotal trial.

The designs of these studies are described briefly herein:

Studies IP631-003 and IP-631-005 (henceforth “Studies –03 and -05”) were virtually identical in design and conduct.

Study -03 was a multicenter, U.S., randomized, double-blind, placebo-controlled, parallel-group study comparing Sanctura 20mg twice daily to placebo twice daily in 523 patients with OAB. Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge), urge incontinence episodes of at least 7 per week, and greater than 70 micturitions per week. The patient’s medical history and urinary diary during the treatment-free baseline period confirmed the diagnosis, signs and symptoms. The co-primary endpoints were change-from-baseline to Week 12 in average daily urinary frequency (referred to as daily number of ‘toilet voids’) and change-from-baseline to Week 12 in average daily urge urinary incontinence episodes as documented in a 7-day voiding diary. One of the secondary endpoints was change-from-baseline in average volume voided per micturition over two days as collected by the patient in each diary period. Additional secondary endpoints included a 4-point urgency severity scale and other quality-of-life questionnaires. In this study, a total of 262 patients received Sanctura 20 mg twice daily and 261 patients received placebo. The majority of patients were Caucasian (85%) and female (74%), with a mean age of 61 years (range 21 to 90 years).

Study –05 was nearly identical in design and procedures to Study –03 except for a minor difference in the classification of endpoints. In this study, there was a single primary endpoint; change-from-baseline to Week 12 in average daily urinary frequency (referred to as daily number of ‘toilet voids’). All other endpoints from Study –03 were again measured, but all as secondary endpoints. In this study, a total of 329 patients received Sanctura 20 mg twice daily and 329 patients received placebo. Again, the majority of patients were Caucasian (88%) and female (82%), with a mean age of 61 years (range 19 to 94 years).

Studies MP94D2.14 and MP94D2.15 (henceforth “Studies –14 and –15”) were 21-day, randomized, placebo-controlled, parallel-group design, European clinical trials. The focus of Study –14 was on urodynamic assessments. Study –15 also included an active comparator.

Study-14 was a multi-center, randomized, double blind, placebo-controlled, parallel- group design in 309 patients with symptoms associated overactive bladder (defined in this somewhat older European study as “urge syndrome” or “detrusor instability”). Patients with urodynamic measurements within 3 months of the start of the study demonstrating those findings consistent with detrusor instability were randomized. Patients were then treated with trospium chloride 20-mg twice daily or placebo for 21 days to a maximum of 28 days. At the end of the 21-day treatment period, all urodynamic measurements were repeated. In this study, micturition diary variables were assessed as a secondary objective. At the study start, patients received 2-day micturition diaries to be completed once weekly for 3 (or four) consecutive weeks. In these diaries, patients were supposed to document the number and volume of micturitions and urge incontinence episodes. A total of 309 patients (including both men and women) were randomized in this trial. Of these, 210 patients (68%) were randomized to receive trospium and 99 patients (32%) received placebo. A total of 262 patients (84.8%) completed the study.

Reviewer’s comment: Sponsor reported that due to various reasons during the trial, not all diaries were returned for evaluation. Therefore, the focus of the review of Study –14 was on the pharmacodynamic endpoints as measured by urodynamics.

Study –15 was a multi-center, randomized, double blind, and double-dummy, placebo and active-controlled trial with three parallel groups conducted in 234 patients at 10 sites in Europe.

The duration of the study was 21 days and the study visits took place on Days -10, 0, 10, and 21. Entry criteria stipulated that all patients have at least an average of 10 daily micturitions and also that they have “urge incontinence and combined forms”. The primary endpoint was number of micturitions per day and secondary endpoints included voided volume and number of urge incontinence episodes. Diaries were kept throughout the treatment period. A total of 234 patients were randomized to trosipium (N=76), active comparator (N=77) or placebo (N=79).

Study MP94D2.04 (henceforth “Studies -04”) was a multicenter, randomized, parallel-arm, double-blind, active-controlled trial for a 53-week treatment duration. Micturition diaries were completed at Baseline, and at Weeks 2, 26 and 52. Micturition diaries were analyzed in 177 patients (130 treated with trosipium and 47 treated with active comparator). Sponsor performed a “retrospective analysis” of key urinary diary variables to compare the two groups.

Reviewer’s comment: The clinical and Biometrics primary reviews revealed significant deficiencies in the collection and analysis of the micturition diary data from Study -04. Therefore, the efficacy data from this trial was not useful in drawing conclusions about the efficacy of trosipium.

4. Clinical results to support the indication

4.1 Efficacy

The efficacy results from both Phase 3, U.S., pivotal efficacy and safety studies (Studies -03 and -05) revealed that Sanctura was associated with clinically relevant and statistically significant reductions in urinary frequency, urge incontinence episodes, and urinary void volume compared to placebo. Table 1 presents the critical efficacy information for Study -03, including the co-primary endpoints change-from-baseline in average daily urinary frequency and average weekly urge incontinence episodes, and the secondary endpoint, average volume voided.

Table 1. Mean (SE) change from baseline to end of treatment (Week 12 or last observation carried forward) for urinary frequency, urge incontinence episodes, and void volume in Study -03.			
Efficacy endpoint	Placebo N=256	Sanctura N=253	p-value
Urinary frequency/24 hours ^{a,*}			
Mean baseline	12.9	12.7	
Mean change from baseline	-1.3 (0.2)	-2.4 (0.2)	<0.001
Urge incontinence episodes/week ^{b,*}			
Mean baseline	30.1	27.3	
Mean change from baseline	-13.9 (1.2)	-15.4 (1.1)	0.012
Urinary void volume/toilet void (mL) ^{a, c}			
Mean baseline	156.6	155.1	
Mean change from baseline	7.7 (3.1)	32.1 (3.1)	<0.001
^a Treatment differences assessed by analysis of variance for ITT:LOCF data set. ^b Treatment differences assessed by ranked analysis of variance for ITT:LOCF data set. ^c Placebo N=253, Sanctura N=248. * Denotes co-primary endpoint ITT=intent-to-treat, LOCF=last observation carried forward.			

In terms of other secondary endpoints, the sponsor developed a 4-point “urgency severity” scale to assess the urgency associated with non-incontinent micturitions, where the scale was: 0=none (no urgency), 1=mild (awareness of urgency, but easily tolerated), 2=moderate (enough urgency discomfort that it interferes with usual activity/tasks), and 3=severe (extreme urgency discomfort that abruptly stops all activity/tasks). This scale was an exploratory measure first used in this particular trial. At baseline, the mean baseline scores for each group was 1.77, reflecting a mild to moderate degree of urgency at baseline. At Week 12, the mean (SE) changes-from-baseline scores were -0.22 (0.03) and -0.04 (0.03) for the Sanctura and placebo groups, respectively.

Finally, the sponsor assessed the effect of Sanctura on the Incontinence Impact Questionnaire, or IIQ, a 30-item, self-reported, health-related, quality-of-life scale designed to assess the impact of urinary incontinence on 4 sub-scales (travel, physical activity, social relationships and emotional health). A modified Incontinence Impact Questionnaire consisting of only 20 items was used in male patients. At baseline, the mean baseline total IIQ scores (for women only) were approximately 202 and 192 for placebo and Sanctura groups, respectively. At Week 12, the mean (SE) change-from-baseline scores were -35.7 (6.9) and -59.1 (6.6) for the placebo and Sanctura groups, respectively. A negative change indicates improvement from baseline. Sponsor stated that this reflected a statistically significant difference between groups. Improvements from baseline in the total IIQ score for males were comparable between groups and not statistically different.

The design and endpoints for *Study -05* were nearly identical to -03 other than there being a single primary endpoint (urinary frequency) for *Study -05*. The results of all three major endpoints are shown in Table 2:

Table 2. Mean (SE) change from baseline to end of treatment (Week 12 or last observation carried forward) for urinary frequency, urge incontinence episodes, and void volume in Study -05.			
Efficacy endpoint	Placebo N=325	Sanctura N=323	p-value
Urinary frequency/24 hours ^{a,*}			
Mean baseline	13.2	12.9	
Mean change from baseline	-1.8 (0.2)	-2.7 (0.2)	<0.001
Urge incontinence episodes/week ^b			
Mean baseline	27.3	26.9	
Mean change from baseline	-12.1(1.0)	-16.1(1.0)	<0.001
Urinary void volume/toilet void (mL) ^{a, c}			
Mean baseline	154.6	154.8	
Mean change from baseline	9.4 (2.8)	35.6 (2.8)	<0.001
^a Treatment differences assessed by analysis of variance for ITT:LOCF data set.			
^b Treatment differences assessed by ranked analysis of variance for ITT:LOCF data set.			
^c Placebo N=320, Sanctura N=319.			
* Denotes primary endpoint			
ITT=intent-to-treat, LOCF=last observation carried forward.			

In terms of other secondary endpoints, the sponsor again assessed the impact of Sanctura on their new, 4-point, Indevus Urgency Severity Scale (IUSS) in this second pivotal study. The sponsor contends that the scale was validated through its use in this trial and in Study -03, and through extensive psychometric testing. At baseline, the mean baseline scores for each group was similar to those seen in Study -03 (1.75 and 1.79 in placebo and Sanctura groups, respectively). At Week 12, the mean changes-from-baseline scores were -0.02 and -0.21 for the placebo and Sanctura groups, respectively.

Finally, the sponsor again assessed the effect of Sanctura on two health-related quality of life questionnaires: the 30-item, Incontinence Impact Questionnaire, or IIQ, and the Overactive Bladder Health-Related Quality of Life Questionnaire, or OAB-q. Results from these supportive secondary endpoints revealed greater numeric improvements in the 4 domains of the IIQ in women treated with trospium than with placebo, and a similar effect in all patients from the OAB-q data.

Reviewer’s comment:

1. **The consistency of the findings across both Phase 3 pivotal trials in the primary and supportive secondary endpoints provides firm support for the efficacy conclusions for this application.**
2. **It remains to be determined whether the new 4-point Indevus Urgency Severity Scale is a validated instrument.**
3. **Sponsor conducted a reverse, stepwise analysis plan for the primary and critical secondary endpoints to determine whether statistical significant differences between groups had been shown at 12 Weeks, 4 Weeks or 1 Weeks. Results of this analysis reveals that for all endpoints (except for urge incontinence episodes in Study -03), there were statistically significant differences at Week 1.**

The sponsor submitted two other trials of note from an efficacy perspective. These were shorter-term, European trials studying urodynamic parameters (-014) and short-term efficacy and safety versus placebo and an active comparator.

Study -014 was a 21 to 28-day, randomized, placebo-controlled trial with the primary objective of assessing the effect of Sanctura 20mg on urodynamic endpoints. The primary efficacy variables were: maximum cystometric bladder capacity (in milliliters) and volume at first unstable detrusor contraction (in milliliters). The secondary efficacy variables included: maximum detrusor pressure at the time of the first unstable detrusor contraction (in cm H₂O), volume of residual urine (in milliliters) and maximum urinary flow (in milliliters per second). The results for the primary endpoints are shown in Table 3:

Table 3: Primary endpoints in Studies MP94D2.14

	Trospium n=177	Placebo n=83	Comparison
Maximum cystometric bladder capacity (ml)			
Baseline: Mean (SE)	222.01 (6.60)	231.95 (9.70)	
Change from Baseline: Mean (SE)	70.7 (8.09)	5.4 (12.82)	65.3 p < 0.01 (t-test)
Bladder volume at first unstable detrusor contraction (ml)	n=173	n=83	
Baseline: Mean (SE)	117.92 (5.35)	114.72 (8.04)	
Change from Baseline: Mean (SE)	97.4 (9.46)	41.4 (9.75)	56.0 p = 0.02 (t-test)

Reviewer's comments:

- 1. The results of this analysis in 260 patients in Study –014 reveals the expected pharmacological effect of trospium: an increase in maximum bladder capacity and bladder volume at the time of the first detrusor contraction. The degree of improvement is considered to be clinically meaningful.**
- 2. The diary data in Study –014 was not adequate to conduct meaningful analysis or draw conclusions.**

Study –015 was a randomized, parallel-arm, placebo and active-controlled, 21-day efficacy and safety trial in 234 patients with OAB. The efficacy endpoints were those traditionally associated with OAB trials, including daily urinary frequency, urge incontinence episodes, and average volume voided. The study was not designed with input from the Division, sample size was small, and the study was not powered for non-inferiority between active treatments. Therefore, the data for the active comparator is not adequate for claims, is not necessary for interpretation of the results of this small trial, and is not shown in this review.

In this trial, the mean (SD) baseline average daily micturitions (urinary frequency) were 12.1 (6.0) and 11.9 (4.9) for the trospium and placebo groups, respectively. The mean (SD) changes from baseline in the IIT population were: -3.4 (4.8) and -1.9 (2.8) in the trospium and placebo groups, respectively. Based upon a fairly small sample size and the number of comparisons made, this difference was not found to be statistically significant. For this same endpoint, however, a per-protocol analysis revealed a significant difference.

For the secondary endpoint, average volume voided, baseline volumes were 122mL (48) and 123mL (46) for the trospium and placebo groups, respectively. The mean (SD) changes from baseline in the IIT population were: +36mL (59) and +19mL (48) in the trospium and placebo groups, respectively. Finally, in those patients who had incontinence episodes at baseline, the number of incontinence episodes decreased on average by 2.9 (N=30, SD=3.1, relative decrease of 73%) for patients treated with trospium chloride and by 1.6 (N=36, SD=2.5, relative decrease of 55%) for patients treated with placebo.

Reviewer's comment: Study –015 provides some measure of support for the efficacy of trospium.

**APPEARS THIS WAY
ON ORIGINAL**

4.2 Clinical Safety

4.2.1 Extent of Exposure

At the time of the original NDA submission, a total of 1775 patients or subjects had been exposed to trospium in studies. At that time there, 1344 patients were exposed in 12 controlled clinical studies, 222 subjects were exposed in 12 clinical pharmacology studies, and 208 patients were exposed in 8 uncontrolled studies.

At the time of the 4-month safety update, and following the submission of the second pivotal study –05, the total number of patients who have been exposed to trospium chloride in all placebo and active-controlled studies increased to 1673 patients. Of these, a total of 1426 received trospium chloride 20mg twice daily. In the two 12-week, pivotal, Phase 3, U.S. efficacy and safety trials and the 9-month, open-label extension, a total of 1181 patients participated. According to sponsor, approximately 407 patients were in the ongoing open-label Phase of the first pivotal U.S. Study.

In all controlled trials combined, 232 patients and 208 patients received trospium for at least 24 weeks and 52 weeks, respectively. A large percentage of this long-term safety data is derived from the 52-week, European, active-controlled study MP94D2.04

Of those patients who received chronic dosing with regimens other than 20mg twice daily, 123 received 40mg twice daily, and 84 received 40mg once daily. Doses in excess of 100mg twice daily and even higher single doses have been administered in Phase 1 studies.

Of note, trospium chloride is has been marketed in various dosage forms (oral and intravenous) and strengths (5mg to 30mg) in at least 19 countries in Europe, the Middle East and Asia. The compound was initially authorized for marketing in 1966. No regulatory authority has refused approval on grounds of safety

Reviewer’s comment: The controlled safety database for Sanctura is adequate by current ICH guidelines. Most long-term safety data is from outside the U.S.; nevertheless, most of the short and medium-term data (12 weeks or thereabouts) are from well-controlled U.S. trials. Most adverse events with trospium, for example, anticholinergic side effects are likely to be seen within 12 weeks of initiating therapy.

4.2.2. Deaths, SAEs and Discontinuations Due to AEs

4.2.2.1 Deaths

At the time of the original NDA submission, a total of 10 deaths were reported within the completed controlled, uncontrolled, and open-label studies: none in the clinical pharmacology studies, 4 deaths in the 12 controlled trials, 4 deaths in the 8 uncontrolled trials and 2 deaths in the ongoing open-label Phase of Study –03.

One patient died in the double-blind phase of Study –05.

This was an 81 year old Caucasian male with significant past medical history of myocardial infarction in 1985, coronary artery bypass surgery in 1994, hypercholesterolemia and glaucoma since 1985, who was hospitalized on day 57 after initiation of the study medication for *hemorrhagic stroke*. CT scan of the head revealed a left parieto-occipital intracranial hemorrhage with surrounding edema and mild mass effect. A carotid duplex scan showed a 15% occlusion of both internal carotids and antegrade flow in the vertebral arteries bilaterally. MRI of the brain revealed intraparenchymal hemorrhage in the left temporal and left parietal areas with

mild intraventricular blood. The hemorrhage was attributed to pre-existing amyloid angiopathy with hypertensive hemorrhage. The study drug administration was permanently discontinued on Day 57 due to the occurrence of this event. The patient was transferred to a nursing home where he died later on Day 125. The investigator judged the event as remotely related to study medication.

In the long-term, active-controlled study MP94D2.04, two patients died, including:

An 89-year old female with cerebral vascular insufficiency, coronary artery disease, cardiac insufficiency and arrhythmia experienced a *stroke* at 41 weeks after starting treatment with trospium. Study drug was stopped. She experienced a second stroke 22 days later and died. The event was judged as not related to study medication.

An 44 year old female experienced lymphadenopathy due to adenocarcinoma of the lungs with metastases to the cervical lymph nodes. She died 10 days after diagnosis from a sudden massive *pulmonary embolism*. The event was judged as not related to study medication.

In a European controlled study, MP94D1.70, one patient died:

A 77-year old male with senile atherosclerosis developed sepsis and hematemesis. He died eight weeks later of acute anemia, hemorrhage of the lower bowel and *diverticulosis*. The event was judged as not related to study medication.

There were 4 deaths in a European uncontrolled study MP94D1.61:

An 86-year old male died of "*unknown causes*" after 56 days on drug. The investigator assessed the event as not related to study drug.

A 97-year old male died of "*unknown causes*" after 13 days on drug. The investigator assessed the event as not related to study drug.

A 78-year old male died of *adenocarcinoma of the prostate*. The investigator assessed the event as not related to study drug.

A 69-year old female died of respiratory insufficiency after a "brain stem attack" 256 days after starting drug. The cause of death was listed as respiratory failure resulting from *stroke due to cerebral metastases of salivary gland tumor*. The investigator assessed the event as not related to study drug.

There were 2 deaths in the open-label Phase of the U.S. trial IP631-003:

A 65-year old female died due to *metastatic lung cancer*. The investigator assessed the event as not related to study drug.

A 62-year old male with a history of coronary artery disease (CAD), angina, s/p coronary artery bypass graft with stenting and peripheral vascular disease was found dead in bed following successful completion of his 3-month double-blind treatment period and more than 3 months of open-label use. Cause of death was listed as *CAD*. The patient had undergone cardiac artery stenting earlier in the same study. The investigator assessed the event as not related to study drug.

At the time of the 4-month safety update, one additional patient died in Study -05:

Patient 13-6313 was a 73-year-old Caucasian male with significant past medical history of congestive heart failure, hypertension, ruptured intestines, colostomy reversal (1997 and 1998), and obesity. On Day 22 (of being on study medication), the patient developed severe nausea and vomiting, abdominal pain, and became weak, dehydrated, and was unable to get out of bed. On Day 23, he was admitted to the hospital and diagnosed with a bowel obstruction. ECG showed normal sinus rhythm, PVC's and right bundle branch block. Laboratory test evaluation revealed renal insufficiency. Chest x-ray was normal. The patient was treated with meperidine, hydroxyzine, metoclopramide, dicyclomine, and famotidine. He also received topical

nitroglycerin paste and verapamil. Cardiac and surgical consults were obtained. During the evening of Day 23, the patient developed shortness of breath and decreased blood pressure. He was diagnosed with myocardial infarction. On Day 24, the patient experienced *cardiac arrest* and subsequently died.

4.2.2.2 Serious adverse events

At the time of the original NDA, in all placebo-controlled trials of trosipium 20mg twice daily combined, there were a total of 9 patients (1.4%) and 19 patients (2.5%) who experienced a serious adverse event (SAE) in the placebo and trosipium groups, respectively. In the trosipium group, these adverse events included: urinary retention (n=3; 0.4%); chest pain (n=2; 0.3%); constipation (n=2; 0.3%); and headache (n=2; 0.3%). In the remainder there was only 1 patient who reported the event and these included: hemorrhagic stroke, cerebrovascular disorder NOS, rash-pustular, tachyarrhythmia, gastroenteritis, electrocardiogram abnormal, ventricular tachycardia, and major depressive disorder, among others.

In all-controlled studies combined, including long-term study MP94D2.04, a total of six (6) SAEs were judged as at least possibly related to treatment with trosipium (including urinary retention, headache, angioneurotic edema, rash non-specific, abscess non-specific, and thirst).

In the ongoing open-label study IP631-003, there were 23 serious adverse events reported and all but three were judged as definitely not related to treatment with trosipium. These were: one report each of heat stroke, bronchitis NOS, and pain NOS.

At the time of the 4-month safety update, the reports of SAEs was updated:

In all placebo-controlled trials of trosipium 20mg twice daily combined, there were a total of 15 patients (1.5%) and 31 patients (2.9%) who experienced a serious adverse event (SAE) in the placebo and trosipium groups, respectively. Therefore, there were an additional twelve (12) SAEs reported in the trosipium group. Of these, only 5 were judged as possibly related to treatment with trosipium and these included one case each of: urinary retention, intestinal obstruction, headache, thirst and myocardial infarction. In all controlled studies, a total of eight (8) new SAEs were judged as possibly related and these included one case each of: urinary retention, intestinal obstruction, headache, thirst, myocardial infarction, angioneuroic edema and rash-erythematous.

4.2.2.3 Discontinuations due to adverse events

At the time of the original NDA submission, discontinuations due to adverse events (AEs) were broken out by safety cohort as follows:

For the pivotal US study -03, the discontinuation rates due to adverse event were 5.7% for placebo (15 patients) and 8.8% for trosipium (23 patients). In this study, the most common reasons for discontinuation was dry mouth (2.3%), constipation (1.5%), abdominal pain NOS (1.5%), urinary retention (1.5%), headache (1.1%), abdominal pain-upper (0.4%), and dizziness (0.4%).

In the long-term, active-controlled trial MP94D2.04, the rates of discontinuations due to adverse events were 7% (n=19) and 11% (n=10) in the trosipium and active control groups, respectively.

In all placebo-controlled studies combined, these incidences were 5.6% for placebo and 7.4% for trosipium with similar AE terms reported in this cohort as in Study -03. For example, in this cohort, the most commonly reported events leading to discontinuation were: dry mouth, headache, urinary retention, constipation, abdominal pain -NOS, and urinary tract infection.

There were several additional discontinuations in uncontrolled studies and these included gastrointestinal symptoms, surgery for perforated appendix, dizziness, elevated LDH level, and bladder outlet obstruction.

At the time of the 4-month safety update, in the combined U.S. pivotal trial, the incidence of discontinuations was 5.1% for placebo and 8.0% for trospium. The actual events leading to discontinuation had not changed qualitatively. The rates and types of adverse events for all placebo-controlled trials combined were similar to the U.S. trials and to those reported in the original NDA. These rates were almost identical to those reported for the all controlled trials combined cohort.

Reviewer's comment: In summary, the incidences and types of serious adverse events and those events leading to discontinuation are consistent with Sanctura's pharmacological action as a potent, non-selective anticholinergic. In this reviewer's opinion, the rates and types of serious adverse events (and discontinuations due to adverse events) are acceptable in view of the treatment effect of Sanctura. Prescribers are generally aware that these sorts of adverse events are possible with anticholinergic agents (events including urinary retention, constipation, headache, intolerance of heat, abdominal pain, and tachycardia).

4.2.3. Overall adverse events

In this reviewer's opinion, the overall adverse terms and incidences from the two pivotal, U.S. Phase 3 OAB trials (Studies -03 and -05) provide the clearest evidence for overall, commonly reported adverse reactions with Sanctura.

In these two studies combined, the incidences of overall adverse events were 62% and 49% for trospium and placebo groups, respectively. The most commonly reported events were those involving the gastrointestinal system (33% for trospium versus 20% for placebo). This finding was driven by two adverse events: dry mouth and constipation. The list of commonly reported adverse events is shown in Table 4 below. This table presents only those events judged as possibly related to treatment by the blinded individual investigator. In addition, the event had to have been reported at a higher incidence in the trospium group than the placebo groups, and by at least 1.0% of patients in the trospium group.

As a comparison, Table 5 provides the adverse events for all placebo-controlled studies (combined), without reference to causality, and reported at an incidence of at least 2.0% in the Sanctura group.

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Table 4. Incidence (%) of adverse events judged at least possibly related to treatment with Sanctura 20mg BID and reported in \geq 1% of all patients treated with Sanctura and more frequently with Sanctura than with placebo in Studies -03 and -05 combined.

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

Abbreviations: BID=twice daily, NOS=not otherwise specified.

Table 5. Incidence (%) of adverse events reported in \geq 2.0% of patients treated with Sanctura (20 mg BID) and more frequent with Sanctura than placebo in all placebo-controlled clinical studies combined

MedDRA BODY SYSTEM/ Preferred term	Placebo (N=969)	Sanctura 20 mg BID (N=1075)
Total patients with TEAEs	419 (43.2)	541 (50.3)
Gastrointestinal disorders		
Dry mouth	61 (6.3)	195 (18.1)
Constipation	35 (3.6)	75 (7.0)
Abdominal pain NOS	17 (1.8)	29 (2.7)
Dyspepsia	14 (1.4)	29 (2.7)
Infections and Infestations		
Urinary Tract Infection NOS	25 (2.6)	34 (3.2)
Nervous system disorders		
Dizziness	20 (2.1)	26 (2.4)

Abbreviations: BID=twice daily, MedDRA=Medical Dictionary for Regulatory Activities, TEAE=treatment-emergent adverse event, NOS=not otherwise specified.

NOTE: This table includes placebo-controlled studies IP631-003, IP631-005, MP94D2.15, MP94D1.60, MP94D1.84, MP94D2.03, MP94D2.14, MP194/18, and MP94D2.01.

It is notable that the 4-month safety updated did not alter the safety conclusions regarding clinical adverse events from the original NDA submission despite the addition of another pivotal study

(20% more patients) and several additional months of open-label safety experience. At the time of the original NDA, the most commonly reported adverse events occurring in all controlled trials, without regard to causality, at a higher rate in drug than in placebo groups, and in at least 2% of the trospium group were:

1. dry mouth (20% - versus 7% placebo)
2. constipation (6% - versus 2.5% placebo)
3. urinary tract infection (5% - versus 3% placebo)
4. dyspepsia (4% - versus 2% placebo)
5. abdominal pain –NOS (3% - versus 2% placebo)
6. dizziness – (2.4% - versus 1.7% placebo)

Additional adverse events in all controlled trials reported by at least 1% of trospium-treated patients and at a higher rate than placebo (all-causality) were: urinary retention, insomnia, urine abnormal NOS, pharyngitis, back pain, vision abnormal NOS, influenza-like illness, and viral infection NOS.

Other adverse events of note from all placebo-controlled studies combined reported at incidences lower than 1%, without regard to causality, and at higher incidences in trospium than in placebo included: supraventricular extrasystoles, tachycardia, eye irritation, vision blurred, myalgia, pain in jaw, urinary disorders (including hematuria, urinary hesitancy, oliguria, micturition urgency), dry throat, dyspnea, urticaria and excema.

Adverse events that occurred at incidences lower than 1%, possibly related to treatment with trospium and higher than placebo in the U.S., Phase 3, pivotal studies included: tachycardia NOS, vision blurred, abdominal distension, vomiting NOS, dysgeusia, dry throat, and dry skin

Additional adverse events reported in the postmarketing period in various countries included: gastritis, palpitations, supraventricular tachycardia, chest pain, Stevens-Johnson syndrome, anaphylactic reaction, syncope, rhabdomyolysis, vision abnormal, hallucinations and delirium, and “hypertensive crisis”.

There are no new adverse events reported after long-term use. The incidences of most reported adverse events in 12-week studies do not change markedly with prolonged use.

Reviewer’s comment: The overall adverse event profile is consistent with the pharmacological effect of trospium chloride as a potent and non-selective anticholinergic agent. In general, this pharmacology can lead to undesired effects on the gastrointestinal, urologic, ophthalmological, cardiovascular, and neurological systems. In the opinion of the reviewer, the types of adverse reactions reported and their incidences are generally acceptable in view of the treatment effect of Sanctura. And, prescribers are believed to be familiar with the anticholinergic side effects of drugs in this class. There were no unexpected or surprising adverse events.

4.2.5 Other safety issues of note

Other safety issues of relevance include:

4.2.5.1. Relationship of age to reported adverse events

The sponsor provided an overall update and analysis of the relationship between age and adverse reactions in the original ISS, the 4-months safety update and in Amendment #28 (dated May 3,

2004). The pivotal studies included a total of 249 patients who were greater than or equal to 65 years of age and a total of 88 patients at least 75 years of age. The sponsor provided the incidences for the most commonly reported anticholinergic adverse reactions broken out by age. Table 6 provides this information:

Table 6. Incidences of commonly reported anticholinergic adverse events by patient age in the pivotal, U.S. Phase 3, controlled clinical trials (rounded to nearest integer) – all-causality.

	<65 years n=342	65-74 years n=161	≥75 years n=88
Dry mouth	18%	21%	31%
Constipation	9%	12%	14%
Dyspepsia	2%	2%	4%
Flatulence	1%	1%	6%
UTI NOS	2%	4%	9%
Dizziness	1%	4%	2%
Urinary retention	1%	2%	3%

From Table 6 it is clear that the incidences of commonly reported adverse events is higher in patients aged 75 years and older. This does not appear to be related to differences in steady-state plasma concentrations, as may be seen in the clinical pharmacologist's primary review. Therefore, it is assumed that this difference reflects an enhanced sensitivity to anti-muscurinic agents in this particular subgroup. Due to small sample size, definitive statistical comparisons between groups cannot be made. Sponsor provided data demonstrating that this increase in incidence doses not result in an increase in severity. Sponsor also provided data from the active comparator arm in Study MP94D2.04 which appeared to demonstrate a similar finding fro dry mouth in the comparator arm. Finally, sponsor agreed that the management of such patients should allow for dose down-titration to 20mg once daily, as was allowed in the pivotal trials and that the Geriatric Use section of the Precautions section would describe this finding.

Reviewer's comment: Based upon the labeling revisions to the Precautions and D & A sections, I find this risk to be acceptably managed in this application.

4.2.5.2. Gender-related safety issues

Adverse events were broken out by gender. Dry mouth was the only commonly reported AE where there was a noticeable difference (approximately 21% in women versus 12% in men). The reader should know that of 6 cases of acute urinary retention, 4 were in males with bladder outlet obstructive symptoms at baseline. This is not entirely unexpected, as the administration of potent anticholinergics to men with outlet obstruction is known to carry this risk.

Reviewer's comment: The overall exposure in male patients is small. Extra caution is appropriate in the management of OAB symptoms in male patients.

4.2.5.2. Potential cardiovascular effects including effect on vital signs and ECGs

Base upon the Division's comments at the time of filing, the sponsor conducted additional analysis of all cardiovascular adverse events in the NDA and submitted this in as a separate

section of the 4-month safety update. In addition, the primary MO carefully assessed each and every cardiovascular AE in the controlled clinical trial database.

All cardiovascular-related MEDRA term adverse events were collected from 2641 patients treated from 3 weeks to 52 weeks in all placebo and active-controlled trials in the NDA. This analysis included 1426 patients, 969 patients, and 246 patients treated with trospium, placebo and active comparator, respectively. The incidences of 41 different adverse events for this “CV cluster analysis” were presented in a single table. The most commonly reported CV adverse events in the trospium group, without regard for causality, were:

1. palpitations 0.9% (placebo = 0.4% and active comparator = 0.4%)
2. chest pain 0.8% (placebo =0.3% and active comparator =0.8%)
3. tachycardia NOS 0.6% (placebo =0.3% and active comparator =0.8%)
4. ECG abnormal NOS 0.5% (placebo =0% and active comparator =0%)
5. Age-indeterminate MI 0.4% (placebo =0.2%, active comparator = 0%)
6. ECG S-T change NOS 0.3% (placebo =0.3%, active comparator =0%)
7. angina pectoris 0.3% (placebo =0%, active comparator = 0%)
8. supraventricular extrasystoles 0.2% (placebo =0.2%, active comparator =0%)

All other events were 0.1% or less in the trospium group. Arrhythmia NOS was actually 0% in trospium group and slightly higher for active comparator (0.4%). MI was 0.2% for trospium, which was the same as placebo, and slightly lower than active comparator 0.8%. Sponsor then broke out the analysis by the individual terms: MI (+age-indeterminate MI), chest pain, angina pectoris, congestive heart failure (CHF), arrhythmias, palpitations and ECG abnormalities.

In terms of *MI*, all three patients in the trospium group had known CAD at baseline, and two required further intervention (angioplasty and CABG) after the adverse event. In terms of age-indeterminate MI, the sponsor’s consultant (Dr. i _____) re-read each set of ECGs for the 6 trospium patients in this category and in each instance, he found there to be “no evidence of any new signal of new morphological findings”. The sponsor found no evidence of trospium being associated with MI.

In terms of *chest pain*, for each and every one of the 11 trospium patients with chest pain, the sponsor believed that these were non-cardiac chest pain cases. For instance, one patient inhaled smoke from a fire, one patient had the chest pain that resolved with continued treatment, one had excessive caffeine intake, one had “atypical chest pain”, one had dyspepsia, one had pain in the breast that resolved with continued treatment, one had wheezing considered non-cardiac in origin, one had intermittent mild chest pain also considered non-cardiac, etc. Of these 11 cases, 5 were considered not related to treatment with trospium by the investigator, one was indeterminate, and the rest were remotely or possibly related. In almost all cases, the chest pain was mild and did not lead to patient discontinuation.

For *angina pectoris*, sponsor commented on each of the four trospium cases. One was double-counted as an MI (see above), one had pre-existing angina and ECG abnormalities at baseline, and two were European reports that were difficult to interpret. Sponsor found no significant difference between groups for this particular adverse event.

There were no cases of *CHF* for trospium.

For all *arrhythmias* combined, the incidence rates between groups were virtually identical (1.1% for placebo and trospium and 1.2% for active comparator). There were no ventricular arrhythmias in the trospium group.

For *ECG abnormalities* reported as AEs, the pooled incidences were virtually identical between trospium (1.5%) and placebo (1.7%) groups. The ECG abnormality types were also similar between groups.

Finally, for *palpitations*, the sponsor acknowledges an overall difference between trospium and placebo, but states that the difference was not seen in U.S. pivotal trials. The sponsor notes that tachycardia and tachyarrhythmia were reported in only 0.6% and 0.1% of patients, respectively, which leads them to believe that the excess number of palpitation events in trospium is not clinically significant.

The sponsor's overall opinion is that there is no difference between trospium and placebo for the most important CV adverse events (MI, angina, CHF, arrhythmia, and ECG abnormalities), that all the chest pain cases were non-cardiac in origin, and that the excess of palpitations is not clinically significant.

Reviewer's comment: I agree with sponsor's overall interpretation, with the caveat that tachycardia, tachyarrhythmia and palpitations are not unexpected adverse events associated with potent anticholinergic therapy. Of greatest importance, there is no evidence to suggest an excess of serious or potentially life-threatening CV events with trospium.

4.2.5.3. Any other potential safety issues

There was no evidence of any effect on laboratory parameters. Mild elevations of serum liver enzymes were rarely reported. There was no evidence that these constituted a direct effect of trospium or a concerning finding.

The incidences rates of somnolence, sedation and drowsiness were fairly low in the Phase 3 trials, however, it cannot be concluded that these rates were comparable to placebo or that they were lower than other drugs in the class. Therefore, caution is still in regard to driving or operating heavy machinery.

All traditional precautions that pertain to systemic anticholinergic medications pertain to trospium, including caution in patients with bladder outlet obstruction, with slow gastrointestinal motility, with glaucoma, and the elderly older than 75 years of age. Further, caution must be used to avoid heat prostration, when imbibing alcohol and when taking other medications that have anticholinergic effects.

5. Major issues from other disciplines or other sources

5.1 Clinical pharmacology and biopharmaceutics

Dr. Kenna provided a 168-page draft final review. She concluded:

“From an OCPB perspective, the application is acceptable given certain changes in the label (as indicated in the review).” This reviewer notes that all OCPB-recommended changes to the label have been successfully accomplished as part of label negotiations.

The following major clinically relevant points were made in this extensive and detailed clinical pharmacology review:

1. The quaternary amine structure is believed to restrict access to the central nervous system and this is *hypothesized* to cause fewer adverse events than those currently approved OAB treatments that do not carry a positive charge.
2. Trospium is not well absorbed. The absolute bioavailability is only approximately 10%. This is probably a consequence of the drug's positive charge and its "reported instability" at $\text{pH} > 4$ (for example, in patients with elevated gastric pH). Approximately 85% of the drug is protein bound at therapeutic concentrations.
3. Seventy percent of the trospium chloride that reaches the systemic circulation is eliminated in urine. Of this, 80% is excreted as unchanged trospium. Thus, approximately 60% is eliminated unchanged. Renal clearance exceeds glomerular filtration rate, indicating that active renal secretion is a significant pathway.
4. Three metabolites have been measured. Breakdown by an esterase to the inactive metabolite, azoniaspironortropanol is the major metabolic route of elimination. Cytochrome P450 enzymes are not predicted to play a major role.
5. Trospium exhibits dose linearity for area-under-the-curve (AUC) but not for maximum concentration (C_{max}). A doubling of the dose (20mg to 40mg) increases the C_{max} 3-fold and a tripling of the dose (20mg to 60mg) increases C_{max} by 4-fold.
6. Multiple dose studies indicate a possible induction of trospium elimination in younger subjects but some accumulation in older subjects. Because single-dose pharmacokinetic parameters are higher in younger than in older subjects, the effects seen after multiple doses serve to "even out" the single-dose differences between age subgroups.
7. High fat meals reduce trospium exposure by 84%. Therefore, dosing on an empty stomach is recommended (as in the controlled efficacy and safety trials).
8. Trospium exhibits diurnal variation in pharmacokinetics; that is, doses taken in the evening yield lower exposures than doses taken during the day.
9. Severe renal insufficiency was associated with a 1.8-fold increase in mean C_{max} and a 4.2-fold increase in AUC relative to healthy subjects. To account for this difference, the recommended dosing regimen in such patients will be 20mg once daily in the evening (as opposed to 20mg twice daily on an empty stomach or one hour before meals). Nevertheless, caution is still advised in this population.
10. Moderate hepatic impairment was associated with a 60% increase in C_{max} and a 15% decrease in AUC, not requiring dose adjustment. There is no information on patients with severe hepatic impairment. Caution is advised in this population.
11. Although no formal drug interaction studies were conducted, in vitro (CYP) studies and results of a population PK model reveal no evidence of metabolic interactions with concomitantly drugs. However, based upon the extent of renal excretion by active secretion, drugs that are renally secreted (including vecuronium, disopyramide, procainamide, clonidine, neostigmine, metformin, and tenofovir) may increase exposure to trospium chloride, or vice versa. Given the reduction in trospium's stability at $\text{pH} > 4$, proton pump inhibitors or antacids have the potential to reduce trospium exposure. Trospium may potentiate the anticholinergic effects of other drugs with such effects, or vice versa.

Similarly, its anticholinergic effect may reduce the efficacy of cholinergic agents and its effect on slowing gut motility may alter the absorption of concomitantly administered drugs. The anticholinergic effect may also enhance the tachycardia associated with drugs that are known to cause tachycardia.

12. Adverse events in Phase 1 and in Phase 3 studies correlated with advanced age (greater than or equal to 75 years of age). This did not appear related to an increase in exposure and may be more reflective of an increased sensitivity of the elderly to the pharmacological effect of anticholinergics. Clinical agrees with OCPB that dose reduction to 20mg once daily following the initial dose of 20mg twice daily would be appropriate based upon the prescriber's assessment of tolerability in a given patient 75 years of age or older. In other Phase 1 studies, adverse event incidences appeared to correlate with exposure, as in food effect, renal insufficiency and hepatic impairment studies.
13. Trospium chloride showed no significant change in corrected QT interval in normal healthy volunteers in a moxifloxacin and placebo-controlled "thorough" QT study. This study included to-be-marketed and supraphysiological doses.
14. The application of a new ink to the marketed tablet required a slight modification in processing compared to the clinical trial material used in Study –003. The sponsor bridging information (dissolution data) to support the equivalence of the to-be-marketed and the Study –03 trial material. Our chemistry reviewer found the dissolution data to be comparable between printed and unprinted tablets.

Reviewer's comment: All clinically relevant OCPB comments have been acknowledged and those that required regulatory action have been resolved. In this reviewer's opinion, there are no clinical pharmacology issues that preclude approval at this time.

5.2 Chemistry

In her draft review of May 25, 2005 (pending team leader sign-off), Dr. Salemme stated:

"From a CMC perspective, this application is recommended for approval."

Dr. Salemme's summary states that all chemistry deficiencies have been adequately addressed. The tradename, Sanctura, is acceptable to the Division of Medication Errors and Technical Support (DMETS). The manufacturing sites have been recommended for approval by the Office of Compliance. The CMC information provided in the application is deemed adequate for demonstrating the identity, quality, purity, and potency of the drug substance and drug product.

5.3 Biometrics

On May 24, 2004, Dr. Meaker provided a brief draft summary of her review. She stated:

"Studies 003 and 005 constitute the basis for my efficacy assessments. They are both prospectively planned, placebo-controlled clinical trials. They were designed to assess the desired clinical endpoints. In both studies, trospium was statistically significantly better than placebo on the primary endpoints of interest. These two studies provide sufficient evidence to support efficacy."

In addition, Dr. Meaker commented that Studies 014 and 015 (non-U.S. studies) provided little additional support for efficacy due to deficiencies in collection of diary data, in pre-defined analysis, and missing data.

5.4 Pharmacology/Toxicology

Dr. McLeod-Flynn's final review stated:

“There are no impediments to approval of this application from a pre-clinical pharmacology/toxicology perspective.”

Dr. McLeod provided comments on labeling with special attention given to the sections on reproductive toxicology, pregnancy and nursing mothers. These were revised to accurately reflect the pre-clinical data and updated to be consistent with the regulations. In summary, there were no effects on fertility in rats at 10X the clinical dose using area-under-the curve (AUC). Further, there were no maternal or fetal effects in a segment II study in rats at 200mg/kg (10X multiple of clinical dose). Similarly, in a rabbit segment II study, there were no maternal or fetal effects at a dose of 50mg/kg (5-6X human exposure). Finally, in the segment II study in rats, the no-effect level for maternal and fetal toxicity was 20mg/kg/day. At 200mg/kg/day, there were signs of maternal toxicity and death. No developmental anomalies were seen at any dose.

There was no evidence of a neoplastic effect in carcinogenicity studies at 10X multiples of average human exposure. There was no evidence of genotoxicity in a battery of assays. There were no histological effects in rats or dogs at any dose tested in general toxicology studies. In rats, these doses exceeded a multiple of 10X and in dogs, the doses exceeded a multiple of 100X.

The only findings of note were attributable to the pharmacological action of the drug and included mydriasis, decreased mucus production, decreased intestinal motility, and increased heart rate.

5.5 Division of Scientific Investigation (DSI)

DSI conducted routine inspections for OAB Study #1 only. Three sites were inspected, including _____ (N=22 randomized) in _____ (N=17 randomized) in _____ (N=14 randomized) in _____ Minor protocol violations and record-keeping inadequacies were noted only at Dr. _____ site, but these were not considered to be of enough significance to adversely affect the acceptability of the data. DSI concluded that the data generated by Drs. _____ could be used in support of the NDA.

5.6 Financial Disclosure

Review of financial certification information by the primary medical officer revealed that the sponsor complied with 21 CFR 54; that is, there was no disclosure of financial interests that could bias the outcome of the trials under NDA 21-595.

5.7 Pediatrics

The sponsor requested a partial waiver for children younger than _____ years of age and such was deemed appropriate and was granted. Sponsor requested a deferral of pediatric studies for children age _____ to 15 years of age and such was granted.

5.8 Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS)

The final assessment by DMETS of the proposed tradename, _____ was completed on February 13, 2004. OPDRA had no objection to the use of the proposed tradename. There was a brief mention of a product called Sancura, a topical benzocaine anesthetic, which is no longer marketed. In their review, OPDRA proposed several changes to the blister, blister carton and container labels. These included:

- 1.
- 2.
- 3.
- 4.
- 5.



The chemistry reviewer assured that all these comments were acknowledged and appropriate revisions were made to this labeling. These issues are resolved.

5.9 Division of Cardio-Renal Drug Products (DCRDP)

Drs. Stockbridge and Throckmorton provided their completed final consult to DRUDDP on April 27, 2004. This consult pertained to the final study report for Study IP631-010, the "thorough" QT study.

DCRDP provided a complete review of this well-designed and adequate thorough QT study. This was a randomized, double-blinded, placebo and active (moxifloxacin)-controlled, parallel group study in 170 generally healthy young (18-45 years of age) subjects. The study employed a multiple-dose design, using the standard dose of Sanctura (20mg twice daily) in one group, and a supraphysiological dose in another (Sanctura 60mg twice daily for two days, followed by 80mg twice daily for two days, followed by 100mg twice daily for one day).

Effects on QT

In this study, a modest QT-prolonging effect of moxifloxacin was demonstrated, indicating assay sensitivity. Trospium was associated with small reductions (not prolongations) of the corrected QT interval using the Fridericia's or individualized correction methods. Dr. Stockbridge concluded that these reductions have no known clinical significance.

T-wave inversions

Only one other issue was of note: new T-wave inversions were seen in this trial, in a greater number of patients in the trospium group, than in either the placebo or moxifloxacin groups. Dr. Stockbridge tallied these as follows: placebo (n=5), moxifloxacin (n=4), low-dose trospium (n=8), high-dose trospium (n=13). Dr. Stockbridge made the following comments about these T-wave inversions:

1. There was very little to suggest a time course following a dose. This may be related to the pK of trospium.
2. Subjects experiencing T-wave inversions tended to be more tachycardic than other subjects of the same groups.
3. A similar pattern of T-wave changes was seen among subjects in all treatment groups

4. Some subjects had T-wave inversions at baseline.
5. One interpretation (by a cardiologist in DCRDP, Dr. Karen Hicks) was that these changes could “probably” represent ischemia unmasked by tachycardia. Dr. Stockbridge did not believe that this was a direct effect of the drug, but rather that the tachycardia could be acting as a “stress in susceptible individuals”.

Acknowledging the review by DCRDP, the clinical review team sought to clarify this issue with sponsor (in conjunction with sponsor’s noted cardiology consultant Dr. _____), and with help from our colleagues in Biometrics. We held an extensive teleconference with sponsor on May 3, 2004 and received a written summary of the issue from sponsor on the same day. The sponsor’s (and Dr. _____) interpretation of the T-wave inversions seen in Study –010 differed from the Cardio-Renal Division’s interpretation.

First, the exact number (and incidence) of patients with new T-wave inversions was somewhat different. Sponsor broke the finding out by day of occurrence (on Day 1 of dosing or on Day 5). The highest numbers were on Day 5, as follows: placebo=4 patients (10%), moxifloxacin=3 patients (8%), trospium low-dose=8 patients (21%), trospium high-dose=9 patients (19%). Sponsor’s analysis included only those with new t-wave inversions (none seen at baseline) and only patients where the T-waves were actually inverted. This data is shown in Table 1, page 6 of sponsor’s May 3, 2004 telefacsimile (Amendment #28 to the NDA).

Reviewer’s comment: The Division asked our Division of Biometrics to conduct an analysis of the data in this same table to assess whether differences between groups was statistically significant. Biometrics responded on May 10, 2004 by eMAIL stating:

“Using the counts from Table 1 (page 6 of sponsor’s May 13, 2004 fax), I find no evidence of a statistical difference between trospium and placebo in the incidence of T wave changes. I used a logistic regression model to compare rates between trospium (20mg) and placebo with period (day 1 or day 5) as strata. The model’s p-value for the drug coefficient was 0.43, indicating no evidence of drug differences. Even including the trospium high-dose results, a drug effect was not significant (p=0.09).”

The sponsor’s comments regarding clinical interpretation of the T-wave findings included:

1. Sponsor referred to these T-wave changes as “non-specific”.
2. Sponsor stated that no clear explanation for this effect was apparent except that the changes may be related to heart rate effects of trospium chloride or a direct non-specific effect that does not appear to be due to an effect on the QT interval duration.
3. The nature of the T-wave inversions observed ranged from flattening to biphasic to a terminal T-wave inversion (sometimes called a reversed check mark pattern). Dr. _____ believed that these configurations were consistent with a non-specific pattern; one more closely associated with a non-clinically significant drug effect, rather than an ischemic effect.
4. No ECG had symmetrical T-wave inversions, the type of T-wave morphology typically associated with ischemia or subendocardial infarction.
5. None of the subjects with T-wave inversions on trospium chloride complained of chest pain. One subject on moxifloxacin complained of “rib pain” and one high-dose trospium patient complained of “heart pounding”.
6. The fact that these patients were young, healthy and carefully screened to exclude signs or symptoms of coronary artery disease (non-smokers, etc) makes it extremely unlikely (“or perhaps near impossible”) that the heart rate changes (up to a maximum of 31 beats per

minute increase from baseline on average, with all heart rates <112 beats per minute) could have caused myocardial ischemia.

7. Dr. _____ concluded:

“Thus, the nature of the study population, degree of heart rate change achieved and the forms of T-wave inversions, in my opinion, virtually exclude any likelihood that myocardial ischemia is present in these subjects. The T-wave inversions observed in this study may have been related to study conditions (these types of changes have been frequently reported from hyperventilation, ingestion of cold fluids) or may be the direct effect of the drug on T-wave morphology. I am not aware of any clinical correlate to T-wave inversions in either of these scenarios. Thus, I have no definitive explanation for the non-specific T-wave changes observed in this study.”

8. Sponsor provided evidence from a previous Phase 1 QT study in which there were no new T-wave inversions in 30 trospium-treated patients (low, or high-dose groups).
9. Sponsor provided evidence from a 52-week, active-controlled trial comparing trospium 20mg twice daily to oxybutynin 5mg twice daily showing only 1 patient with a new T-wave inversion (trospium-treated patient, incidence=0.5%) compared with none on oxybutynin.
10. Sponsor provided evidence from the first U.S. Phase 3 study (Study -003) that demonstrated no difference between placebo and trospium for new T-wave inversions. These were seen in 3 patients (1.2%) on trospium and 2 patients (0.8%) on placebo. This finding was later confirmed in an analysis of the second U.S. Phase 3 study (Study -005).
11. Sponsor concluded:
“The imbalance of T-wave inversions seen in study IP631-010, a trial of normal, healthy volunteers, was not observed in the other normal volunteer trial (IP631-001), no in trials conducted in the target population (IP-003 and IP631-002/MP94D2.02). Therefore, T-wave inversions observed on trospium chloride in the “Thorough ECG Trial: IP631-010 are non-specific and had no clinical consequence.

Reviewer’s comment: Based on all the above evidence, this reviewer agrees with Dr. _____ that one cannot conclude that these new T-wave inversions reflect myocardial ischemia. Instead, I agree with sponsor that these are non-specific changes that may not even be directly related to trospium itself. The labeling should reflect this finding from Study -010 and should also provide some degree of clinical interpretation.

5.10 Division of Drug Marketing, Advertising and Communications (DDMAC)

In her formal consult, Corrine Kulick of DDMAC provided 7 pages of comments in regard to the draft labeling. Rather than reiterate all these comments here, the reviewer refers the reader to the consult. Suffice to say here that the clinical review team carefully assessed each and every comment in the DDMAC review and made all appropriate and clinically relevant changes to the label. Based upon our successful labeling negotiations, all these items were resolved.

6. Regulatory summary

At this time, I recommend that Sanctura should be granted marketing approval for the OAB indication. There are no outstanding issues.

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

/s/

Mark S. Hirsch
5/27/04 04:40:21 PM
MEDICAL OFFICER

Daniel A. Shames
5/27/04 05:32:20 PM
MEDICAL OFFICER

MEMORANDUM

May 26, 2004

TO: File

FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 21-595

I have reviewed the action package and the proposed final label for Sanctura (trospium chloride) and concur that the application may be approved based on the pharmacology/toxicology data. Concerning the issue of including information obtained in a nonclinical (rat) study on distribution of the drug across the blood-brain barrier, I concur with the review division that this is not appropriate for inclusion in the product label..

|S|

Kenneth L. Hastings, Dr.P.H.
Associate Director for Pharmacology and Toxicology
Office of Drug Evaluation III

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

/s/

Kenneth Hastings
5/26/04 05:36:20 PM
PHARMACOLOGIST

Cutright, Dale

From: Beam, Sammie
t: Monday, May 24, 2004 2:43 PM
Cutright, Dale
Subject: RE: Trospium- pending NDA

Hi,

It takes 2 to 4 weeks to do a final review on a name. We typically ask for a consult for a final review. I do see that the consult for the original review was valid until about 5/13/04. That is close enough in time that DMETS can pass on doing a final review.

Sammie

-----Original Message-----

From: Cutright, Dale
Sent: Monday, May 24, 2004 2:31 PM
To: Beam, Sammie
Subject: Trospium- pending NDA

Sammie:

Please run the trade name, Sanctura, again before the Friday action date.

Thanks,

Dale

Dale Cutright
Regulatory Project Manager
JDP/HFD-580
ER/FDA
Phone: 301-827-4260
Fax: 301-594-0747

MEMORANDUM OF CONFERENCE

DATE: May 4, 2004

APPL NUMBER: NDA 21-595- trospium chloride

SPONSOR: Indevus

ATTENDEES:Name: Mark Hirsch, M.D., Team Leader
Suresh Kaul, M.D., Medical Officer
Dale Cutright, Regulatory Project Manager, DRUDP
Evelyn Farinas, Safety Evaluator, Office of New Drugs, (OND)
Paula Gish, Safety Evaluator, OND
Melissa Truffa, Safety Evaluator Team Leader, OND
Florence Houn, M.D., M.P.H., Office Director, Office of Drug
Evaluation (ODE III)
Julie Beitz, M.D., Supervisory Medical Officer

SUBJECT: Pre-Approval Safety Conference (PSC)

Two pivotal studies were conducted to assess the safety and efficacy of Sanctura (trospium chloride) for the treatment of patients with overactive bladder with symptoms of urge incontinence, urgency, and frequency. The results were discussed.

This New Molecular Entity (NME) is an anticholinergic prescribed twice daily at 20 mg. The most prevalent side effects include dry mouth, constipation, headache, abdominal pain, and urinary retention.

There was discussion about trospium having increased anticholinergic side effects in patients older than 75, and such will be mentioned in the labeling.

The labeling for cholinesterase inhibitors, such as Aricept, indicates that anticholinergic agents may interfere with the efficacy of Aricept (or vice versa). It was suggested that the Division consider similar labeling for the drug/drug interaction section of the trospium label.

It was stated that long term safety studies have not shown any surprising or unexpected effects.

Action Item

Consideration will be given to revising the Precautions, Drug Interactions section of the trospium label in regard to cholinesterase inhibitors.

Dale Cutright
Regulatory Project Manager

Mark Hirsch, M.D.
Team Leader