

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 3rd, 2004

From: Suresh Kaul, MD
Medical Officer
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-595 (study IP631-003 and IP631-005)

I have reviewed the financial disclosure information submitted by Indevus Pharmaceuticals, Inc. in support of their NDA 21-595 for Sanctura (Trospium Chloride)

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 number and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study IP631-003 Trospium Chloride 20-mg oral twice daily in Patients with OAB. A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel group Study Conducted in the US.	Study Start date 11/07/01 Study End Date 09/06/02	Appropriate documentation received, no financial disclosure submitted

Study Number/Title	Study Status	Financial Disclosure Review
Study IP631-005 Trospium Chloride 20-mg oral twice daily in Patients with OAB. A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel group Study Conducted in the US.	Study Start date 6/05/2003 Study End Date 01/06/2004	Appropriate documentation received, no financial disclosure submitted

Documents Reviewed:

- Financial Certification Information (Form FDA 3454) submitted August 13, 2003 and February 5, 2004.

Study IP631-003

Study IP631-003 was started November 7, 2001 and completed September 6, 2002. There were 490 principal investigators and sub-investigators at 55 sites (523 patients) in this trial. Financial disclosure information was received for all investigators; none had any disclosable information.

Study IP631-005

Study IP631-005 was started June 5, 2003 and completed January 6, 2004. There were 412 principal investigators and sub-investigators at 59 sites (658 patients) in this trial. Financial disclosure information was received for all investigators; none had any disclosable information.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of both pivotal trials (IP631-003 and IP631-005) in NDA 21-595.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Suresh Kaul
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MEDICAL OFFICER

The sponsor was asked to comment on how to handle these geriatric patients who did not tolerate trospium 20-mg twice daily. Lowering the dose to 20-mg once daily might be an option.

Sponsor and Division agreed to continue to discuss this issue internally and mutually.

Question #2.

We have carefully reviewed the QT study -010 conducted to study the effects of trospium on cardiac repolarization and conduction. Although, there was no effect on QT prolongation, there was evidence of an increased number of patients with new T-wave inversion when compared to the other control groups. The sponsor was asked about the clinical significance of t-wave inversion seen in this trial and whether it could be related to ischemia or a of stress pattern to tachycardia resulting from trospium.

The sponsor stated that they had looked at the previous QT study-001 and the pivotal trial 003, and the results had been re-read by a central ECG Lab. Sponsor noted no significant difference in T-wave morphology for trospium versus control groups as evaluated by ECGs in these studies. The results could be submitted tomorrow.

The sponsor's consultant, Dr. _____, stated that the issue of T-wave inversions on Day 1 between groups was not concerning, saying that it did not reflect cardiac ischemia or any strain pattern on heart. He re-enforced that these changes could be from variety of other reasons other than ischemia. It was stated that these were healthy individuals without coronary disease who experienced no symptoms and were very unlikely to be experiencing ischemia at the time of real T-wave changes. Further, Dr. _____ believed that this could be a direct effect of trospium on ECG morphology as seen with a variety of other drugs. The heart rate change induced by trospium in this study was not large enough to induce ischemia in this healthy population. In addition, _____ stated that the shape of T-wave inversion seen with trospium in the IP631-010 study was not of a shape associated with ischemia.

As an aside, FDA asked Dr. _____ why there seemed to be more variability in ECG measures on the baseline day in study IP631-010. _____ said it was not due to the study design. This may be due to just random influences on ECGs.

The sponsor will summarize this discussion and submit it to the application promptly.

/s/

Dale Cutright
Regulatory Project Manager

/s/

Mark Hirsch, M.D.
Team Leader

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/s/

Mark S. Hirsch
5/25/04 08:17:31 AM

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)



NDA 21-595

INFORMATION REQUEST LETTER

3-4-04

Indevus Pharmaceuticals, Inc.
Attention: Bobby W. Sandage, Jr., Ph.D.
Executive Vice President
99 Hayden Avenue, Suite 200
Lexington, MA 02421-7966

Dear Dr. Sandage:

Please refer to your April 28, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trospium Chloride 20 mg Tablets.

We are reviewing the submission dated February 6, and the corrected version dated February 10, 2004, of the Study IP631-010, ("A Single Site Single-Blind Randomized Placebo and Positive Controlled, Parallel Designed Study of the Electrocardiographic Effects of Oral Trospium Chloride (20 mg BID Steady State and Supratherapeutic Levels) in Healthy Men and Women Volunteers: a Definitive or Thorough QT Trial"), and have the following information requests. Submit a prompt response so that we may continue our evaluation of your NDA. Additionally, raw data are requested in SAS Transport file format.

QT Study Results:

Note that the following terminology is used in this letter:

QTcF refers to Fridericia corrected QT interval
 Δ QTcF refers to baseline corrected QTcF

QTcI refers to Individual corrected QT interval
 Δ QTcI refers to baseline corrected QTcI

QTcB refers to Bazett corrected QT interval
 Δ QTcB refers to baseline corrected QTcB

1. The QT data from multiple leads were provided in your February 10, 2004 submission. Please clarify which lead provided the data used in the analysis submitted on February 10, 2004.

2. Provide the QT and concentration data in a SAS data file with the following columns:

Subject
Dose
Day of sample
Nominal time
Nominal time since first dose
Concentration
ECG Lead
RR
QT
QTcF
QTcI
QTcB
Gender of subject

3. Provide a SAS data file with the following columns:

Subject
Maximum Dose of trospium
Cmax Day 1
Cmax Day 5

4. Provide the data in the table "PK1" with an additional column indicating the dose of drug.

5. In addition to the analyses provided in the study report, please perform the following analyses of the ECG data.

(a) Mean analyses

- i) Provide mean QTcF at Tmax with 95% confidence intervals for each study arm.
- ii) Provide mean Δ QTcF at Tmax with 95% confidence intervals for each study arm.
- iii) Provide mean QTcI at Tmax with 95% confidence intervals for each study arm.
- iv) Provide mean Δ QTcI at Tmax with 95% confidence intervals for each study arm.
- v) Provide mean QTcB at Tmax with 95% confidence intervals for each study arm.
- vi) Provide mean Δ QTcB at Tmax with 95% confidence intervals for each study arm.

Note that in calculations (i)-(vi), baseline and placebo QTc for the analysis of trospium response should be time matched for trospium Tmax.

(b) Outlier analyses

- i) Number of observations of Δ QTcF between 30 and 60 msec for each study arm
- ii) Number of observations of Δ QTcF > 60 msec for each study arm
- iii) Number of observations of QTcF > 450 msec for each study arm
- iv) Percent of observations of Δ QTcF between 30 and 60 msec for each study arm
- v) Percent of observations of Δ QTcF > 60 msec for each study arm
- vi) Percent of observations of QTcF > 450 msec for each study arm

Provide the same analyses for QTcI and QTcB.

NDA21-595

(c) Provide confidence intervals on the results reported in the "ECG Results" table on Page 11 of the study report.

In addition to these requests regarding Study IP631-010, provide information to support a dosing regimen in subjects with:

- (a) Moderate renal impairment
- (b) Mild renal impairment

If you have any questions, please call Dale Cutright, Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
3/4/04 03:24:20 PM



NDA 21-595

2-11-04
3 mo extend.

Indevus Pharmaceuticals, Inc.
Attention: Bobby Sandage, Jr., Ph.D.
Executive Vice President, Research and Development
99 Hayden Avenue, Suite 200
Lexington, MA 02421-7966

Dear Dr. Sandage:

Please refer to your April 28, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trosipium Chloride 20 mg Tablets.

On February 9, 2004, we received your February 6, 2004 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 28, 2004.

If you have any questions, please call Dale Cutright, Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
2/11/04 04:04:41 PM
Chief, Project Management Staff

MEMORANDUM OF TELECON

DATE: February 6, 2004

APPL NUMBER: NDA 21-595- trospium chloride

BETWEEN:

Name: Indevus Pharmaceuticals, Inc.
Gwen Reis, Senior Director of Regulatory Affairs

Phone: 781-402-3406

AND

Name: Dale Cutright, Regulatory Project Manager, DRUDP

SUBJECT: The acceptance criteria for the Dissolution test used to test the drug product at release and during stability.

The testing for dissolution should be done at 30 minutes, not at —minutes (which was used to sample the NDA batches.)

The acceptance criterion for the dissolution test should read: $Q = \text{—}\%$ in 30 minutes

The sponsor was asked to confirm that they accept testing at 30 minutes, to send us that confirmation by fax, followed by official submission, and to provide an amended release specification and stability specification for trospium chloride drug product reflecting this change.

Dale Cutright
Regulatory Project Manager

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/s/

Dale Cutright
2/9/04 07:35:03 AM
CSO

MEMORANDUM OF TELECON

DATE: January 28, 2004

APPL NUMBER: NDA 21-595– trospium chloride

BETWEEN:

Name: Indevus Pharmaceuticals, Inc.
Greg Lerch, Ph.D., Chemist
Gwen Reis, Senior Director of Regulatory Affairs

Phone: 781-402-3406

AND

Name: Kate Meaker, M.S., Statistician, Division of Reproductive and Urologic
Drug Products (DRUDP)
Jean Salemme, P.D., Chemist, DRUDP
Dale Cutright, Regulatory Project Manager, DRUDP

SUBJECT: Location of SAS data sets for Study 14
Revision of Comparability Protocol for post-marketing change in
container

The sponsor was contacted and requested to identify the location of the folder for the urodynamic variables analysis for Study #MP94D2.14. It was explained by the sponsor that the extreme values found in Study #MP94D1.15 were due to two patients using incorrect start values, thus the data has been reanalyzed. The sponsor will analyze the data for Study #MP94D2.14 and requested information will be forthcoming.

The sponsor was also directed to the comparability protocol submitted for post approval of the NDA, in the event the sponsor desires a new vendor and changes the container closures, HDPT bottles and caps. The protocol, as submitted, was in a difficult format to evaluate, and the sponsor was requested to resubmit the information with the headings: Type of change, Required Testing; and Supporting Documentation. They were also told to make the description short and specific. The sponsor indicated that this protocol presentation was contracted out to a packaging expert and they would be contacted and requested to re-do the format.

The sponsor also indicated that the previously requested stability data would arrive at the Agency the week of February 9.

Dale Cutright
Regulatory Project Manager

MEMORANDUM OF TELECON

DATE: January 20, 2004

APPL NUMBER: NDA 21-595– trospium chloride

BETWEEN:

Name: Indevus Pharmaceuticals, Inc.
Bobby Sandage, Jr., Ph.D., Executive Vice President
Greg Lerch, Ph. D., Chemist
Gwen Reis, Senior Director of Regulatory Affairs

Phone: 781-402-3406

AND

Name: Leslie Kenna, Ph. D., Clinical Pharmacologist, Division of Reproductive and Urologic Drug Products (DRUDP)
D.J. Chatterjee, Ph.D., Clinical Pharmacologist, DRUDP
Dale Cutright, Regulatory Project Manager, DRUDP

SUBJECT: Clarification of BCS classification and solubility issues.
(Reference: Telephone conversation dated January 15, 2004.

- BCS Classification

The sponsor has indicated, based on the information they have obtained, that the drug may be classified as a BCS level 3 compound. It has low permeability—about 10% of the drug is absorbed. It is a quaternary amine that is freely soluble in water. Dissolution data verifies that 20 mg dissolves in 250 mL of various media (e.g. water, phosphate buffer). The solubility data has been submitted in Amendment #1 (dated May 28, 2003) in the CMC section of this NDA where they compared the dissolution profile of printed and unprinted tablets in various media.

The Agency agrees with the sponsor that the results establishing this drug as a BCS Class III may not be relevant for this submission. However, the sponsor has already conducted the necessary permeability experiments (in addition to the solubility results included in this application) and may submit the permeability results in the future in another submission.

- Dissolution specifications

The dissolution specifications will be sent in an amendment to the NDA on January 20, 2004.

- Dosing in renal impairment

PK simulations suggest that once every other day dosing may be appropriate for dosing to renally impaired subjects. The C_{max} is still higher in renally impaired, but no accumulation. Simulations predict no greater side effects with this regimen.

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/s/

Dale Cutright
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/s/

Leslie Kenna
1/21/04 07:36:57 PM

MEMORANDUM OF TELECON

DATE: January 16, 2004

APPL NUMBER: NDA 21-595- trospium chloride

BETWEEN:

Name: Indevus Pharmaceuticals, Inc.
Gwen Reis, Senior Director of Regulatory Affairs

Phone: 781-402-3406

AND

Name: Dale Cutright, Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP)

SUBJECT: Specific questions from Clinical Pharmacologist and Medical Officer

A telephoned call was made to the Sponsor to ask the following questions:

- Clinical Pharmacologist (Leslie Kenna, Ph.D.)

We would like information regarding the BCS classification of trospium chloride. Please indicate where information on the solubility of trospium chloride at different pH values is located in the NDA.

Medical Officer (Suresh Kaul, M.D.)

- Are there any renal clearance studies done due to the anticholinergic effect being more pronounced in 2 groups, (1) 65-75 age and (2) 75 and up age?

/s/

Dale Cutright
Regulatory Project Manager

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/s/

Dale Cutright
1/21/04 02:50:54 PM



Indevus
Pharmaceuticals, Inc.

99 Hayden Avenue, Suite 200
Lexington, MA 02421-7966
Tel: (781) 861-8444
Fax: (781) 861-3830
www.indevus.com

January 13, 2004

Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation III, Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
JAN 14 2004
FDR/CDER

Reference: **NDA 21-595**
Trospium Chloride:
Amendment # 8
Request for Partial Waiver of Pediatric Studies (Children less than 5 years of age)
Request for Deferral of Pediatric Studies (Children 5 to 15 years of age)

N-000-PU

Dear Dr. Shames:

In accordance with provisions under the Pediatric Research Equity Act of 2003, Indevus has enclosed two requests, one for a partial waiver and one for a deferral of the requirements to conduct clinical studies in pediatric subjects.

If you have any questions, please contact me at (781-402-3406), Gwyn Reis (781-402-3422) or Greg Lerch (781-402-3420).

Best regards,

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

MEMORANDUM OF TELECON

DATE: January 7, 2004

APPL NUMBER: NDA 21-595- trospium chloride

BETWEEN:

Name: Indevus Pharmaceuticals, Inc.
Bobby W. Sandage, Jr., Ph.D. VP, Regulatory Affairs
Gwen Reis, Senior Director of Regulatory Affairs

Phone: 781-402-3406

AND

Name: Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP)
Dale Cutright, Regulatory Project Manager, DRUDP

SUBJECT: Notification of DMETS recommendation to not use _____
Status of Reviews/Response to December, 2003 letters
Expected submission date of study report for December QT study
Pediatric waiver request
Outstanding inspections
Labeling

Background:

The sponsor was telephoned with an NDA review status update, as follows:

Discussion:

Trade Name

- It has been recommended in a DMETS consult dated December 9, 2003, that the proposed trade name, _____ should not be used. DMETS believes that _____ has look-alike and sound-alike potential with _____. The clinical implications of such an error are clear. The sponsor will submit the results from the _____ studies for review along with an alternate name and will request an expedited review. The Agency will not be sending a letter on this issue, unless requested by the Sponsor. (The Sponsor called later the same day to inform the Division that the results of the _____ studies will not be submitted, instead a new proposed trade name will be submitted next week.)

Review Status

- A complete response to the Division's December 31, 2003 information request letter is expected the week of January 12, 2004. This will include chemistry and clinical pharmacology information.
- The clinical pharmacologist has concerns regarding the dose to administer in severely renal impaired patients.
- The statistical and clinical reviews are underway. It is considered crucial that the results from Studies MP94D2.14 and MP94D2.15 support Study IP 631-003. At a minimum, the Division would like to see a second study where trospium provides clinically meaningful benefit for toilet voids in order to support efficacy.
- Anticholinergic side effects appear worse in older patients. For this group of patients, dose adjustment may be necessary.

QT Study

- Sponsor informed the division that active dosing in the controlled QT study was concluded on December 23, 2003. Analysis of the large number of ECGs is underway. Submission of the data is expected on February 8, 2004. The sponsor is aware that the submission is likely be treated as a major clinical amendment.

Pediatric

- A request for waiver of pediatric studies for ages 6- and deferral of studies for ages < 15 will arrive next week. The Division commented that this plan is appropriate.

Inspection

- The sponsor informed the division that the Germany manufacturing site is to be inspected on January 30 and the inspection will last for one week.

Label

- The sponsor inquired whether the Division could begin its review of the label. The division has not yet begun its labeling review. Depending on the status of the individual discipline reviews, some parts of the label could be discussed with the sponsor prior to completion of all reviews.

/S/

Dale Cutright
Regulatory Project Manager

/S/

Mark Hirsch, M.D.
Medical Team Leader

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/s/

Mark S. Hirsch
1/23/04 04:47:08 PM



NDA 21-595

12-31-03

Indevus Pharmaceuticals, Inc.
Attention: Bobby W. Sandage, Jr., Ph.D.
Executive Vice President
99 Hayden Avenue, Suite 200
Lexington, MA 02421-7966

Dear Dr. Sandage:

Please refer to your April 28, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trosipium Chloride 20 mg Tablets.

We are currently reviewing your submission and have the following comments and requests for additional information:

Clinical Pharmacology:

- Indicate where the raw *in vitro* dissolution profile data on the batch used in Study IP631-003 and the raw *in vitro* dissolution profile data for the to-be-marketed batches are located in the NDA.
- Provide the following additional data from Study MP94D2.02 (“Pharmacokinetics and Bioavailability of Trosipium Chloride in Patients with Renal Impairment in Comparison with Healthy Volunteers after Administration of an Oral Dose of 40 mg”): append a column indicating each subject’s creatinine clearance and renal clearance value to the data file “SD_D2_02” submitted to the FDA on September 30, 2003.
- Provide the raw PK and PD data (metabolite data in addition to trosipium chloride data if available) for each subject who participated in Study MP94D2.11. Please provide the data for all subjects—regardless of whether they completed or were removed from the study (i.e. include the data from subject — 07).

Clinical:

- Indicate where in your submission the validation materials for the modified Incontinence Impact Questionnaire (IIQ) may be found. If those materials have not been previously submitted, please provide them.

Chemistry:

- We are currently reviewing your proposal for a Comparability Protocol for container/closures and the acceptance criterion for the dissolution test. Agreements regarding them will be conveyed to you at a later time.

-

- The proposed limits for _____ azoniaspironortropanol, and total impurities in the drug product specification are not in accordance with ICH guidelines. The limits should be based on the values obtained from the calculation for the mean plus three standard deviations for the clinical batches and currently manufactured batches. The calculations done with the _____ month/25°C stability data show that the drug product specification should be revised as follows. Revise the drug product specification to show that the limit for _____ is NMT _____, the limit for azoniaspironortropanol is NMT _____ and the limit for total impurities is NMT _____.

- Regarding the fact that during stability studies the trospium chloride drug substance occasionally fails to meet the acceptance criterion of the clarity of solution test, we request the following:

Provide additional information to demonstrate that the failures in the clarity of solution test are not an indicator of reduced quality of the trospium chloride drug substance.

- When the tradename that will be proposed for the trospium chloride tablets is known, provide a copy of the carton label for review.

Pharmacology:

- Regarding the rat tumor data submitted in study # _____ -431827, please submit clarification of the classified causes of death in the rat study, explaining discrepancies between rat and mouse classifications, so that we may finalize the statistical review of the rat carcinogenicity study.
- In addition, please submit a dataset containing the re-reading of slides for lung neoplasms that also identifies the animal number for each case of neoplasm.

If you have any questions, please call Dale Cutright, Regulatory Project Manager, at (301) 827-4260.

Sincerely,


{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
(HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
12/31/03 10:36:13 AM
Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 15 2003

Dear Dr. _____

Between September 24 and 30, 2003, Ms. Courtney Long, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #IP631-003 entitled: "A Multicenter, Double-Blind, Placebo-Controlled Study of 20 mg, Twice Daily Trosipium Chloride for 12 Weeks Followed by a 9-Month, Open-Label Treatment Phase in Patients with Overactive Bladder") of the investigational drug trosipium chloride, performed for Indevus Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Long during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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/s/

Khin U
12/18/03 03:25:07 PM



Food and Drug Administration
Rockville MD 20857

DEC - 8 2003

Dear Dr. _____

Between August 11 and September 2, Ms. Kelly Moore, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #IP631-003 entitled: "A Multicenter, Double-Blind, Placebo-Controlled Study of 20 mg, Twice Daily Trosipium Chloride for 12 Weeks Followed by a 9-Month, Open-Label Treatment Phase in Patients with Overactive Bladder") of the investigational drug trosipium chloride, performed for Indevus Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

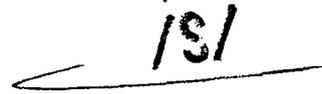
From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection Ms. Moore presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not adhere to the protocol [21 CFR 312.60]. The protocol requires pregnancy tests to be performed on blood or urine samples collected at the Day 84 visit. These pregnancy tests were not performed for subjects 6495 and 6647.
2. You did not maintain adequate and accurate records [21 CFR 312.62(b)] in that discrepancies were observed between source records and electronic case report forms including, but not limited to, discrepancies in vital sign measurements, void amounts, void times, and medical histories for subjects 6228, 6230, 6233, 6371, 6382, 6494, and 6644.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Moore during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,



Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

FEI: 3004090805

Field Classification: VAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

Deficiencies noted:

- failure to adhere to protocol (5)
- inadequate and inaccurate records (6)

Deficiency Codes: 5 and 6

cc:

HFA-224
HFD-580/Doc.Rm. NDA #21-595
HFD-580/Rev Div Dir/Shames
HFD-580/MO/ Kaul
HFD-580/PM/Cutright
HFD-46/47c/r/s/ GCP File #011006
HFD-46/Blay
HFR-SW240/DIB/Miller
HFR-SW2520/Bimo Monitor/Thompson
HFR-SW2520/Field Investigator/Moore
GCF-1 Seth Ray

r/d: KMU:11/26/03

reviewed: 11/26/03:12/1/03

f/t:sg:12/3/03

c:/data/royblay/vai letters/ _____ ?

o:\blay\s _____

Reviewer Note to Rev. Div. M.O.

14 subjects were randomized to the study with eleven subjects completing the double-blind portion of the study. Consent forms for all subjects were reviewed. All patient records were reviewed in depth for completeness, visit schedule compliance, laboratory results, and study outcome. Data at this site appear acceptable in support of the relevant submission.

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/s/

Khin U
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NDA 21-595

12-5-03

Indevus Pharmaceuticals, Inc.
Attention: Bobby W. Sandage, Jr., Ph.D.
Executive Vice President
Research and Development
99 Hayden Avenue, Suite 200
Lexington, MA 02421-7966

Dear Dr. Sandage:

Please refer to your April 28, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trospium Chloride 20 mg Tablets.

We have completed our review of your Protocol IP 631-010 submitted November 21, 2003, and the overall study design is acceptable, however, the following comments regarding dosing, sampling, and data analysis should be considered:

1. Ensure that an adequate number of subjects complete the 60 mg and 80 mg dosing arm to assure assessment of trospium chloride QT effects at supratherapeutic exposures expected in a clinical setting (e.g. exposure increases due to intrinsic or extrinsic factors such as renal impairment, drug interactions, etc.) Your concerns regarding dropouts for this regimen may be circumvented by administering a single high dose (e.g. 200 mg) to obtain information at high exposures.
2. Previously submitted data suggest that exposure (e.g. C_{max}) to trospium chloride may be greater after a single dose of trospium chloride than exposure to a dose of the same strength following intake of multiple doses of that strength. It is, therefore, recommended that additional PK samples be collected. PK sample collection is recommended on the first day that each of the 20 mg, 60 mg, and 80 mg doses are administered. One important PK characteristic to capture is the maximum concentration for each arm at each dose. Additionally, trough levels should be collected during the study.

When selecting time points for PK sampling, consider that t_{max} may differ for the therapeutic and supra-therapeutic doses of trospium chloride. In addition, consider that inter-individual variability in t_{max} may require collection of PK samples at multiple time points around the mean and/or median t_{max}.

3. Meal times have been selected to reduce the effect of food intake on trospium chloride absorption. An additional consideration in devising a meal schedule is the effect of meals on QT interval. It has been reported that intake of meals may prolong the QT interval. Given that moxifloxacin and trospium chloride achieve C_{max} at a different time, meals may confound the QT effect observed on any study arm in a parallel study. Sponsor should factor this in to the study design and analysis.

4. We recommend that the primary analysis be defined as the change in Fridericia corrected QT interval (QTcF) at the time of maximum drug concentration. Given the possibility of a decrease in exposure over time, the maximum concentration may occur on Study Day 1, Study Day 3 (when titrated up from 60 mg to an 80 mg dose), or on Study Day 5.

We recommend that you refer to the Concept Paper (“THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS”; available on the FDA’s website at www.fda.gov) for information on additional analyses that are recommended, such as computing maximum QTc.

A time averaged change in QTc may underestimate QT liability.

5. You propose to discontinue any subject whose QTc measure exceeds 500 msec or any subject who is observed to have a change in $QTc > 60$ msec during a dosing interval.

We recommend that the entire profile of QTc measures, PK samples, and other planned assessments be collected in every individual regardless of QTc response. We recommend that the decision regarding whether to receive the next dose planned after such an outlying value is measured not be automatic, but be at the discretion of the study investigator. The study investigator should decide if such measures were spurious, for example, due to QT measurement error.

Report on such incidences and include such subjects’ data in the study report.

We recommend that subjects with extreme QTc measures be evaluated for genetic factors contributing to the response.

6. We recommend that a formal statistical hypothesis testing procedure be defined. We recommend that formal statistical testing be performed to exclude the possibility of a change in baseline corrected QTcF relative to placebo of 5 msec and that the one-sided 95% confidence interval on that estimate exclude 10 msec (i.e. fall below 10 msec). We recommend this analysis be performed for Study Day 1, Study Day 3 (when the dose is increased from 60 mg to 80 mg), and Study Day 5 unless Day 5 alone is representative of clinically relevant supratherapeutic exposures (refer to comments #1 and #2).

7. Enroll enough subjects on each arm to assure that Study IP631-010 will detect the effect described (above) in recommendation #6 with at least 80% power. Provide power calculations with the study results.

8. We recommend a double blind study. We also recommend that the number of tablets be equivalent for all study arms. Placebo tablets may be used to assure that all subjects receive the same number of tablets at a given dose time. Additionally, placebo tablets dosed in the evening can resolve any potential concern regarding having moxifloxacin dosed QD while trospium chloride is dosed BID.

9. Protocol IP631-010 indicates that outliers will be evaluated with respect to the number of subjects with an outlying measurement. Protocol IP631-010 does not indicate that outliers will be tallied with respect to the number of events. We recommend that the outlier analysis include both approaches. To be specific, we recommend that outlier tables for each arm of the study be provided to show what is listed below in points (i)-(xii). Note that the following terminology is used:

QTc refers generically to corrected QT interval

(QTc includes, for example, Fridericia, individual, and other correction methods)

Δ QTc refers to baseline corrected QTc

$\Delta\Delta$ QTc refers to baseline and placebo corrected QTc

- (i) Percent of subjects with Δ QTc between 30 and 60 msec
- (ii) Percent of subjects with Δ QTc > 60 msec
- (iii) Percent of subjects with QTc > 450 msec
- (iv) Percent of observations of Δ QTc between 30 and 60 msec
- (v) Percent of observations of Δ QTc > 60 msec
- (vi) Percent of observations of QTc > 450 msec
- (vii) Number of subjects with Δ QTc between 30 and 60 msec
- (viii) Number of subjects with Δ QTc > 60 msec
- (ix) Number of subjects with QTc > 450 msec
- (x) Number of observations of Δ QTc between 30 and 60 msec
- (xi) Number of observations of Δ QTc > 60 msec
- (xii) Number of observations of QTc > 450 msec

We recommend that the outlier analysis be performed with respect to Fridericia corrected QT interval and any other correction methods of interest. We recommend that the outlier analysis be performed for all subjects and also separately for males and females.

10. In evaluating outliers, perform the aforementioned calculations (Recommendation #9, parts (i)-(xii)) on the raw measures of QTc. That is, outlier analysis should not be performed on the mean of the replicate measures collected at a given time point in a given subject. Each measurement should be evaluated on its own.

11. Consider performing the study in an age-matched population.

12. Consider measuring metabolite concentration if there is reason to believe that metabolites of trospium chloride may prolong the QT interval. One way this may be beneficial is in its contribution to a valid concentration-response analysis.

13. Submit the raw data collected in every subject (including those who do not complete the study) from Study IP631-010 in SAS transport file format. The dataset should include the following columns:

NDA 21-595

Page 4

Subject ID, Dose, Day of Sample, Nominal Time of sample, Measured time of sample, QT, QTcF, QTcI, RR, Plasma concentration of drug, Plasma concentration of metabolite(s), subject age, gender of subject. If available, provide the creatinine clearance for each subject as a column in the dataset, as well.

If you have any questions, please call Dale Cutright, Regulatory Project Manager, at (301) 827-4260.

Sincerely,


{See appended electronic signature page}

Daniel Shames, M.D.

Director

Division of Reproductive and Urologic Drug Products
(HFD-580)

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 18 2003

Issued
11/24/03
NDA
21595

Dear Dr. _____

Between September 9 and 16, 2003, Ms. Karen McNabb-Noon, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #IP631-003 entitled: "A Multicenter, Double-Blind, Placebo-Controlled Study of 20 mg, Twice Daily Trospium Chloride for 12 Weeks Followed by a 9-Month, Open-Label Treatment Phase in Patients with Overactive Bladder") of the investigational drug trospium chloride, performed for Indevus Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator McNabb-Noon during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/s/
Joseph P. Salęwski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

Page 2 - _____

FEI: 3002995252

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

cc:

HFA-224
HFD-580/Doc.Rm./NDA # 21-595
HFD-580/Division Director/Shames
HFD-580/MO/Kaul
HFD-580/PM/Cutright
HFD-47/c/r/s/ GCP File #010136
HFD-47/Blay
HFR-NE250/DIB/Kravchuk
HFR-NE250/BIMO Monitor/Madigan
HFR-NE250/Field Investigator/McNabb-Noon
GCF-1 Seth Ray

r/d:rab/10/24/03
reviewed: JPS: 10/30/03
f/t:ML: 11/2/03

Reviewer's Note to Review Division's Medical Officer

17 subjects were randomized to the study. Raw source documents and electronic CRFs were reviewed for each of these subjects including, but not limited to, medical histories, drug accountability, concomitant medications, and adverse events. The data appear acceptable in support of the relevant submission.

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/s/

Joseph Salewski
11/24/03 09:48:51 AM

MEMORANDUM OF TELECON

DATE: November 13, 2003

APPL NUMBER: NDA 21-595– trospium chloride

BETWEEN:

Name: Indevus Pharmaceuticals, Inc.
Bobby W. Sandage, Jr., Ph.D. VP, Regulatory Affairs

Phone: 781-402-3406

AND

Name: Leslie Kenna, Ph.D., Clinical Pharmacology and Biopharmaceutics
Reviewer, Division of Reproductive and Urologic Drug Products
(DRUDP)
Dale Cutright, Regulatory Project Manager, DRUDP

SUBJECT: Clarification of the Agency's current correspondence of November 6, 2003 concerning Study IP631-001 ("A Placebo-Controlled Trial of Trospium Chloride on QTc Interval in Health, Normal Subjects Following Steady-State and Single Oral Dosing").

Background:

The new NDA for trospium chloride, submitted by Indevus Pharmaceuticals, located in MA, is a new chemical entity (20mg. Tablet) indicated for the symptoms associated with overactive bladder, a condition characterized by symptoms of urinary frequency, urgency, and urge incontinence. This NDA was received on April 29, 2003.

Included with that submission is Study IP631-001 ("A Placebo-Controlled Trial of Trospium Chloride on QTc Interval in Health, Normal Subjects Following Steady-State and Single Oral Dosing").

The Agency communicated questions regarding said study to the sponsor in a letter dated November 6, 2003. The sponsor initiated a communication requesting clarification of "#7. Perform the following analyses of the ECG data", including a)-d) subparts in said letter.

Discussion:

Sponsor asked the reviewer (Kenna) to clarify several plots of the data requested. Specifically, how the plot requested in Question 7b(i) in the letter to Indevus dated November 6, 2003 differed from the plot requested in Question 7b(ii) in said letter.

After clarification, the sponsor mentioned that their response to the November 6, 2003 letter will be submitted in a few days and that the Agency will see that there is considerable variability in their data.

Sponsor also mentioned that due to what they've heard about the current climate at the FDA regarding concern about QT prolongation potential, they are concerned that this issue could potentially delay approval. Sponsor said that they plan to submit a protocol for another prospective QT evaluation study with the response to the November 6, 2003 letter. Sponsor said the aim is to complete this additional QT evaluation study within this review cycle. The reviewer (Kenna) stated that the purpose of the letter sent to Indevus on November 6, 2003 was to allow the Agency to gather as much information as possible from the data Indevus already collected. The reviewer stated that the November 6, 2003 letter was not meant to be interpreted as a request for an additional study.

/S/

Dale Cutright
Regulatory Project Manager

/S/

Leslie Kenna, Ph.D.
Pharmacokinetics Reviewer

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/s/

Dale Cutright
11/25/03 06:35:56 AM
CSO

Leslie Kenna
11/25/03 09:09:48 AM
BIOPHARMACEUTICS

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: January 15, 2004	DESIRED COMPLETION DATE: February 15, 2004 PDUFA DUE DATE: February 27, 2004	ODS CONSULTS #: 04-0014
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TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Dale Cutright
Project Manager
HFD-580

PRODUCT NAME: Sanctura™ (Trospium Chloride Tablets) 20 mg	NDA SPONSOR: Indevus Pharmaceuticals, Inc.
NDA: 21-595	

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

RECOMMENDATIONS:

- DMETS has no objections to the use of the proprietary name Sanctura. If the approval of the application is delayed beyond 90 days from the signature date of this review, the name, Sanctura, and its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.
- DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.
- DDMAC finds the proprietary name Sanctura acceptable from a promotional perspective.

/S/	/S/
_____ Carol Holquist, RPh Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664	_____ Jerry Phillips, RPh Associate Director Office of Drug Safety Center for Drug Evaluation and Research Food and Drug Administration

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 12, 2003

NDA # 21-595

NAME OF DRUG: Sanctura™
(Trospium Chloride Tablets) 20 mg

NDA HOLDER: Indevus Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products, to review the proprietary name Sanctura regarding potential name confusion with other proprietary and established drug names. Labels and labeling have been submitted for review and comment. Additionally, an independent study conducted by _____ was submitted in support of the proprietary name Sanctura.

This is the second proposed proprietary name for this application. _____ was initially submitted for review however, DMETS did not recommend the use of this name (see ODS consult 03-194).

PRODUCT INFORMATION

Sanctura (Trospium Chloride) is an antispasmodic, antimuscarinic agent. Sanctura is indicated for the treatment of patients with overactive bladder associated with symptoms of urge urinary incontinence, urgency, and urinary frequency. The usual dose is 20 mg twice daily taken on an empty stomach. Sanctura is supplied in blister strips, _____ tablets per strip, _____ blister packs per carton, and in 60 and 500 tablet count bottles.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Sanctura" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.⁴ An expert panel discussion

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/main/trademarks.htm>

was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written inpatient prescription studies and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Sanctura. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified the proprietary names, Sarafem and Cardura as having the potential for confusion with Sanctura. These products are listed in Table 1 (see below), along with the dosage forms and usual dosage.
2. DDMAC did not have concerns about the name Sanctura with regard to promotional claims.

**Table 1
Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel**

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Sanctura	Trospium Chloride Tablets 20 mg	Oral: 20 mg twice daily	N/A
Sarafem	Fluoxetine Hydrochloride Capsules 10 and 20 mg	Initial treatment: 20 mg/day given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle). Maintenance/Continuation treatment: 20 mg/day given continuously and up to 3 months at a dose of 20 mg/day given intermittently for an additional 3 months.	LA
Cardura	Doxazosin Mesylate Tablets 1 mg, 2 mg, 4 mg, and 8 mg	Hypertension: 1 to 16 mg once daily. Benign Prostatic Hyperplasia: 1 to 8 mg once daily.	LA
Sancura	Benzocaine Topical Anesthetic	No longer marketed	LA,SA
* Frequently used, not all-inclusive. ** L/A (look-alike), S/A (sound-alike)			

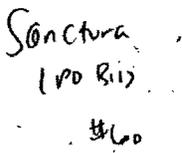
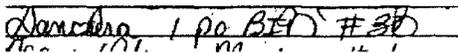
B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. The entered search term is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The results from the Sanctura queries did not indicate any additional product names that had strong phonetic or orthographic similarities to Sanctura.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for each proposed proprietary name to determine the degree of confusion of Sanctura with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written for each name, each consisting of a combination of marketed and unapproved drug products and a prescription for Sanctura (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> 	<p>Sanctura Tablets One by mouth two times a day Dispense #60</p>
<p><u>Inpatient RX:</u></p> 	

2. Results:

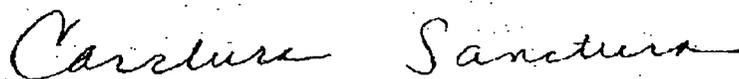
None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S product. See appendix A for the complete listing of interpretations from the verbal and written studies.

3. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Sanctura, the primary concerns raised were related to potential confusion with the currently marketed products Cardura and Sarafem. The name Sancura was also identified as having the potential to look and sound similar to Sanctura. However, upon further review it was discovered that the product Sancura is no longer marketed. Additionally, several product differences between Sancura and Sanctura, such as dosage form, route of administration, dosing schedule, and strength, also helped to diminish DMETS concerns with this name pair.

DMETS conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Sanctura could be confused with currently marketed products. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of interpretations from the verbal and written prescription studies were phonetic or spelling misinterpretations of the drug name Sanctura.

- a. Cardura and Sanctura may look similar when scripted. Cardura contains doxazosin and is indicated for the treatment of hypertension and benign prostatic hyperplasia. The first letter "C" in Cardura may look similar to the first letter "S" in Sanctura as do the letters "ar" versus "an", respectively. Additionally, the letter "d" in Cardura may look similar to the letters "ct" in Sanctura if the loop of the letter "d" is not fully closed. The remaining letters "ura" in each name is identical. Although Cardura and Sanctura share a similar dosage form and route of administration, the products differ with respect to many other characteristics such as strength, dosing regimen (once daily vs. twice daily), and usual dosage (1 to 16 mg vs. 20 mg). These differences should minimize confusion that may result from look-alike similarities with the names.

Handwritten cursive script showing the words "Cardura" and "Sanctura" side-by-side. The letters are fluid and connected, illustrating potential visual similarities between the two names when written in a cursive style.

- b. Sarafem and Sanctura may share some look-alike properties. Sarafem contains fluoxetine and is indicated for the treatment of premenstrual dysphoric disorder. Sarafem and Sanctura both begin with the letters "Sa" and share the similarly scripted letter "r" versus "n", respectively. If the loop of the letter "a" in Sarafem is not fully closed, it can look similar to the letter "c" in Sanctura. The ending of each name (fem vs. tura), however, is distinguishable when scripted (see below). Although Sarafem and Sanctura share a similar dosage form, route of administration, and strength (20 mg) the differences in look-alike properties and dosing schedule (one a day vs. twice daily) minimize confusion.

Handwritten cursive script showing the words "Sanctura" and "Sarafem" side-by-side. The letters are fluid and connected, illustrating potential visual similarities between the two names when written in a cursive style.

4. _____ STUDY

Indevus Pharmaceutical contracted _____ to evaluate the name candidate Sanctura. The sample study for the study consisted of 200 medical professionals that included urologists, primary care physicians, obstetrician-gynecologists as well as community and institution-based pharmacists. The research methodology used by _____ includes handwritten prescriptions by pharmacists, comprehensive, computerized research and analysis of drug names in the US marketplace that may be considered similar, and review of all safety data by and independent Professional Review Committee. The objectives of the methodology were to evaluate whether a proposed proprietary name for a drug or device may be prone to confusion in prescribing and dispensing, and to assess whether the name makes claims that are exaggerated, false, misleading or fanciful.

Per _____ study results, no exaggerated, false, misleading or fanciful claims were identified. The following names were identified as having a potential for look-alike and/or sound-alike similarity: Cardura, Carnitor, Centurion Az, Dura-Vent, Dura-Vent/A, Dura-Vent/DA, Duricef, Ridaura, Salutensin, Sancura, Sandimmune, Sandostatin, Sanestro, Sangcya, Sanguis, Sanhist T.D. 12, Sanorex, Sansert, Sanstress, Santyl, Sectral, Se-Cure, Senexon, Singulair, Sinupan, Sinutrol, Sinuvent, Solurex, Solurex LA, Strattera, and Surelac. These names were further reviewed and were found to have minimal potential for confusion with Sanctura.

DMETS Response

DMETS concurs with _____ findings that the potential for confusion between Sanctura and the names mentioned above is minimal. The name Sancura was also identified by the Expert Panel in DMETS, however, the name was thought to have minimal potential for confusion with Sanctura upon discovering that the product is no longer marketed. Additionally, other product differences between Sancura and Sanctura, such as dosage form, route of administration, dosing schedule, and strength, diminish the risk of confusion.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

In the review of the draft blister and container labels as well as carton labeling of Sanctura, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. BLISTER LABEL

1. _____
2. _____

B. BLISTER CARTON LABELING

- 1.
2. _____
3. _____

4. _____

C. CONTAINER LABEL

1. _____

2. _____

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Sanctura. If the approval of the application is delayed beyond 90 days from the signature date of this review, the name, Sanctura, and its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.
- B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Sanctura acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Alina R. Mahmud, R.Ph.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

