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/s/

Alina Mahmud
2/13/04 03:41:01 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/13/04 03:56:22 PM
DRUG SAFETY OFFICE REVIEWER

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

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

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

A-7

NDA 21-595
Sanctura

Post Marketing Commitments

No other postmarketing commitments other than pediatrics (see pediatric page).

I

**APPEARS THIS WAY
ON ORIGINAL**



NDA 21-595

11-6-03

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.

In the process of reviewing Study IP631-001 ("A Placebo-Controlled Trial of Trospium Chloride on QTc Interval in Healthy, Normal Subjects Following Steady-State and Single Oral Dosing"), several questions have emerged. Your response to each of these items is requested. Additionally, raw data are requested in SAS Transport file format.

Note that the following terminology is used in this letter:

QTcF refers to Fridericia corrected QT interval

Δ QTcF refers to baseline corrected QTcF

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

1. Justify why no positive control (e.g. orally administered moxifloxacin 400 mg) was used in this study. Can you provide evidence of assay validity without a positive control?

2. How was the dose selected?

Please justify the selection of doses used in Study IP631-001.

3. Tabulate the mean and range of exposures (C_{max} , AUC) expected when dosing trospium chloride to subjects with reduced elimination capacity. Situations to separately address include:

a) drug-drug interactions (e.g. another renally secreted drug)

b) mild renal impairment

c) moderate renal impairment

d) severe renal impairment

e) mild hepatic impairment

f) moderate hepatic impairment

g) severe hepatic impairment

h) in elderly subjects

Indicate the source of the data used to address each circumstance.

4. How was the sample size selected?

5. Please provide power calculations for each part ((a) the single dose study and (b) the multiple dose study) of Study IP631-001.

e.g. Assuming a 5% error rate, what is the power to detect a $\Delta\Delta\text{QTcF}$ of 5 msec for the sample size used?

6. How were the ECG sampling times selected?

Explain the rationale for the timing of ECG measurement.

7. Perform the following analyses of the ECG data.

a) Provide 90% and 95% confidence intervals:

i) on the estimate of mean ΔQTcF for every study arm

ii) on the estimate of mean $\Delta\Delta\text{QTcF}$ for each of the trospium chloride study arms

b) Provide plots of mean QTcF (and standard deviation bars) as a function of concentration (not C_{max}) for:

i) each arm such that all data from a given arm are pooled

ii) each arm such that the data from *each subject* on a given arm are pooled

c) Provide plots of mean ΔQTcF (and standard deviation bars) as a function of concentration (not C_{max}) for:

i) each arm such that all data from a given arm are pooled

ii) each arm such that the data from *each subject* on a given arm are pooled

d) Provide plots of mean $\Delta\Delta\text{QTcF}$ (and standard deviation bars) as a function of concentration (not C_{max}) for:

i) each arm such that all data from a given arm are pooled

ii) each arm such that the data from *each subject* on a given arm are pooled

e) Provide outlier tables for each arm of the study:

i) Percent of subjects with ΔQTcF between 30 and 60 msec

ii) Percent of subjects with $\Delta\text{QTcF} > 60$ msec

iii) Percent of subjects with $\text{QTcF} > 450$ msec

iv) Percent of observations of ΔQTcF between 30 and 60 msec

v) Percent of observations of $\Delta\text{QTcF} > 60$ msec

vi) Percent of observations of $\text{QTcF} > 450$ msec

vii) Number of subjects with ΔQTcF between 30 and 60 msec

viii) Number of subjects with $\Delta\text{QTcF} > 60$ msec

ix) Number of subjects with $\text{QTcF} > 450$ msec

x) Number of observations of ΔQTcF between 30 and 60 msec

xi) Number of observations of $\Delta\text{QTcF} > 60$ msec

xii) Number of observations of $\text{QTcF} > 450$ msec

8. Provide the raw data collected from Study IP631-001 (“A Placebo-Controlled Trial of Trospium Chloride on QTc Interval in Healthy, Normal Subjects Following Steady-State and Single Oral Dosing”) in SAS transport file format. We specifically would like the following: Subject ID, Treatment, Dose, Day of Sample, Nominal Time of Sample, Measured Time of Sample, QT, QTcF, RR, Plasma Concentration of Drug, Plasma Concentration of Metabolite(s), Gender of Subject.

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
11/6/03 11:51:48 AM



FILING REVIEW LETTER

NDA 21-595

7-10-03

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 also refer to a telephone conversation on April 15, 2003 between Drs. Salemme and Lin, Ms. King and Ms. Reis concerning Manufacturing and Controls, a telephone conversation between Ms. Cutright and Ms. Reis regarding the status of a trade name, and your submissions dated May 28, 2003 and June 13, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 27, 2003 in accordance with 21 CFR 314.101(a).

The following comments relate to the filing review of the Human Pharmacology and Bioavailability/Bioequivalence section:

- Please provide data relevant to the Human Pharmacology and Bioavailability/Bioequivalence section in SAS transport file format. The studies of specific interest are MP94D2.13 MP94D2.05, MP94D2.10, MP94D4.02, MP94D2.07, MP94D2.12, MP94D2.08, MP94D2.11, MP94D2.02, IP631-004, MP194/68, and MP194/26.
- The population PK study (IP631-004) suggests a potential interaction between trospium chloride and CYP 2C9 inhibitors. The significance of this result will be a review issue. The need for a drug-drug interaction study to investigate the result further will also be a review issue.
- An investigation of the effect of trospium chloride on QT interval was provided. Whether or not the results are clinically significant will be a review issue.
- Bridging information linking the clinical trial and to-be-marketed formulations has been provided. These data will be reviewed in detail.

The following review issues, which are not an impediment to NDA filing, have been identified by the Pharmacology/Toxicology reviewer:

- The statistical review for the carcinogenicity studies is still outstanding. The statistician is conducting an analysis which incorporates survival data and historical data.
- 
- The proposed labeling section of the NDA did not contain information about multiples of human exposure (AUC or body surface area) in the reproductive toxicology section.

The following comments relate to the review issues of the Clinical section:

- In Study IP631-003, we note that the reported incidences of chest pain and urinary retention were both 2.3% in the trospium chloride group and 0.4% in the placebo treated group. Although the clinical significance of these findings cannot be determined at this time, they are of concern to the Division. Please submit a summary of safety from the NDA for these two specific adverse events and also provide special focus on the individual cases from Study IP631-003 with reference to causality, severity, outcome, duration of event and resolution.
- In Study IP631-003, we note that the change-from-baseline in the average number of incontinence episodes were -1.98 for placebo and -2.20 for trospium chloride. When you compared these results using rank ANOVA – ITT:LOCF for the difference between the groups, you report that the difference was statistically significant ($p=0.0118$). When our clinical review team did a preliminary analysis of this data using a comparison of means and an analysis of variance, we did not find statistical significance. Please be aware that the Division of Biometrics will conduct its own analysis. Nevertheless, we request that you cite the specific location in the NDA where we may find the original finalized statistical analysis plan, the specific analysis that you conducted for the incontinence endpoint, and if there are any differences between these two. Further, we request that you cite the location in the NDA where we might find additional information to support a beneficial effect of trospium chloride on incontinence episode frequency.
- You report that a total of 208 patients were exposed to trospium for at least 1 year and 232 patients were exposed for at least 6 months. The number of subjects who were exposed for at least 6 months appears to be lower than that required in ICH guidance. If you do not agree with this assessment, please state why the number of subjects exposed to the drug is sufficient for conducting an adequate safety review.
- We note that Study MP94D4.04 was prematurely terminated. Please provide the rationale for terminating this study. If the study was discontinued for safety reasons, please provide details as to the nature of the safety concern that led to the study termination.

The following comments relate to the Chemistry section:

- To clarify the request made to you during the April 15, 2003 telephone conversation, the full dissolution profiles (sampling at multiple time points) for the NDA batches, both the commercial printed tablets and the unprinted tablets, obtained at release and during stability should be submitted to the NDA. These profiles will be reviewed to establish the appropriate Q value for the dissolution acceptance criterion. Full dissolution profiles will not be required for future stability batches. Post-approval batches placed on stability will only require sampling at the dissolution time point that is approved in the application.
- In Figure 4-7 in the drug product section of the electronic submission, dissolution profiles for batch 904349 are compared to batch A0013763. Please describe these batches, i.e. the formulation of each, the manufacturing scale for the manufacture, and explain the similarity between these batches and the primary stability (printed or unprinted) tablets.
- The stability data provided for the unprinted tablets in PVC blisters show that at _____ some tablets failed the specification for water content (loss on drying), hardness, and some individual impurity content. Stability data for the printed tablets in Aclar blister, a proposed alternate blister packaging, are provided for _____. To determine if the Aclar blisters are comparable to the PVC blisters with respect to protecting the drug product from moisture permeation, please provide the _____ stability data for the printed tablets in the Aclar blister packs.
- We acknowledge that a 24-month expiry is proposed for printed tablets in the containers of _____cc bottle, _____cc bottle, PVC blister, and Aclar blister. The dissolution study provided in the NDA to link the unprinted tablets with the printed tablets applies to the drug product in the _____cc bottle, _____cc bottle, and PVC blister. Whether the limited stability data provided for the drug product in the Aclar blister will be sufficient to justify the same expiry will be determined during the review.

We are providing the above comments to give you preliminary notice of potential review issues. Our review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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
7/10/03 05:01:03 PM



IND 61,381

7-9-03 IR.

Indevus Pharmaceuticals, Inc.
Attention: Gregory Lerch
Vice President, Regulatory Affairs & Pharmaceutical Science
99 Hayden Ave., Suite 200
Lexington, MA 02421-7966

Dear Mr. Lerch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for trospium chloride.

We also refer to your amendment dated April 3, 2003 (serial # N-042). We have completed the Biometrics review of your submission and have the following statistical comments and recommendations. Please note that these requests are not clinical hold issues. However, response to them is requested.

1. The Validation Report for the Urgency Severity Scale presents a retrospective evaluation of the Indevus Urgency Severity Scale (IUSS). It does not sufficiently address all the relevant issues for validating a scale as an efficacy endpoint. A particular issue is that the IUSS has only very weak correlations to the three clinical endpoints recommended by the Division. This report does not support using the IUSS as a primary endpoint.
2. The Sample size calculation for the IUSS is not relevant since the IUSS is not acceptable to the Division as a primary endpoint.
3. The statistical Plan to Assess Time on Onset of Treatment Effectiveness in Overactive Bladder lists the three endpoints requested by the Medical Officer: Frequency of Toilet Voids, Frequency of Urge Incontinence, and Volume Voided. These should be co-primary endpoints. The study should be designed to show efficacy is achieved for all three endpoints at the same time.
4. The timing of efficacy data collection is inappropriate for a time to onset claim. Specifically, evaluations are only collected at Week 1, 4, and 12. The reverse stepwise analysis proposed could be applicable if data were collected and analyzed for all weeks of the study.
5. The Statistical Plan describes using Per Protocol or Completers analyses. This could be proposed as a secondary analysis. The primary analyses should be based on the Intent-to-Treat (ITT) population with Last Observation Carried Forward (LOCF), not the alternatives listed. The analyses would have to demonstrate that the LOCF procedure does not bias the statistical analyses in favor of the active treatment.

IND 61, 381

Page 2

If you have any questions, call Jean King, M.S., R. D., 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
7/9/03 04:40:21 PM



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

PHARMACOLOGY/TOXICOLOGY MEMO

NDA NUMBER: 21-595
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 04/26/03
DRUG NAME: Trospium Chloride
INDICATION: Overactive Bladder
SPONSOR: Interneuron Pharmaceuticals, Inc.
REVIEW DIVISION: Division of Reproductive and Urologic Drug Products (HFD-580)
PHARM/TOX SUPERVISOR: Lynnda Reid, Ph.D.
DIVISION DIRECTOR: Daniel Shames, M.D.
PROJECT MANAGER: Dale Cutright
RECOMMENDATION: The Pharmacology and toxicology data supports approval of this NDA. There are no outstanding issues.

Trospium chloride is an anticholinergic, muscarinic receptor antagonist, quaternary ammonium derivative of tropine. Muscarinic receptor antagonists prevent the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle, and gland cells; in peripheral ganglia; and in the central nervous system. Due to its quaternary ammonium structure and hydrophilic properties, trospium chloride does not cross the blood-brain barrier. Dr. McLeod-Flynn has provided a comprehensive review of the submitted pharmacology and toxicology studies. The primary significant effects were attributable to the pharmacological action of the drug and include mydriasis, decreased mucus production, decreased intestinal motility, and increased heart rate.

No evidence of genetic toxicity was observed in a battery of assays including Ames tests, mouse lymphoma assay, and an in vivo rat micronucleus assay. Two-year carcinogenicity studies in rats and mice were conducted by the sponsor and reviewed by the ExecCAC. The studies were considered acceptable. There was no evidence of tumorigenicity. There was no evidence of impaired fertility.

Comparisons to human dosing for the reproductive toxicity studies were made on an exposure (AUC) basis. Fetal effects were only observed at maternally toxic doses and no effects were observed at AUC concentrations corresponding to expected human exposures. There was no evidence of teratogenicity in either rats or rabbits. I concur with the recommended Pregnancy Category C based on only a 10 fold exposure multiple between doses producing maternal and fetal toxicity in animals and expected doses in women.

Less than 1% of the administered trospium chloride was excreted into the milk of lactating rats. There was a slight decrease (nonsignificant) in the number of surviving neonates on post partum days 4 and 7 from litters exposed to 10 fold higher multiples of the drug than expected in women.

Labeling changes have been proposed for the Pregnancy and Nursing Mothers sections of the label.

45 DAY MEETING CHECKLIST FOR NDA 21595

FILEABILITY:

On initial overview of the NDA application: there is no impediment to filing from a Pharm/Tox perspective.

PHARMACOLOGY AND TOXICOLOGY:

- (1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin? YES
- (2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review to begin? YES
- (3) On its face, is the pharmacology section of the NDA legible so that substantive review can begin? YES
- (4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetics studies, etc)? YES
- (5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the marketed product or to explain why such repetition should not be required? YES
- (6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57? Multiples of human exposures in terms of AUC or body surface area should be given, in addition to nominal doses, in the Pregnancy section.
- (7) Has the sponsor submitted all special studies/data requested by the Division during Pre-submission discussions with the sponsor? YES
- (8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted rationale to justify the alternative route? YES
- (9) Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? YES (Many studies were performed in the 80's, but were adequate for interpretation by modern standards; explanations of deviations were listed.)
- (10) Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? YES (Deviations from modern standards appear to be minimal and not to result in any question of scientific integrity. No overall statement regarding animal welfare was submitted, but modern study protocols were reviewed by an animal welfare committee.)
- (11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. YES

Reviewing Pharmacology Officer

Date

Supervisory Pharmacology Officer

Date

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/s/

Laurie McLeod
6/24/03 02:14:44 PM
PHARMACOLOGIST

Alexander W. Jordan
6/26/03 11:08:44 AM
PHARMACOLOGIST

NDA 21-595
Sanctura

Nonclinical Inspection Review Summary

Not applicable for this application.

**APPEARS THIS WAY
ON ORIGINAL**

Filing Memo

NDA: 21-595
Compound: Trospium Chloride
Sponsor: Indevus Pharmaceuticals, Inc.

Date: June 12, 2003
Reviewer: Leslie Kenna, Ph.D.

Background:

This NDA for the new chemical entity, trospium chloride, includes the results of 8 controlled (6-placebo, 2-active) phase III clinical studies (IP631-003, MP94D2.04, MP94D2.14, MP94D2.15, MP94D4.04, MP94D2.03, MP94D4.03 and MP94D1.73). Study IP631-003 was performed in the United States while the other 7 were performed in Europe. Study IP631-003 is the pivotal clinical trial.

This NDA contains the results of a population PK study (Study #IP631-004)—a trial conducted in patients who enrolled in the pivotal trial and elected to participate in a subsequent 9-month open-label trial.

This NDA includes the results of ten single dose PK studies in healthy volunteers (MP94D2.05, MP94D2.10, MP94D4.02, MP94D2.07, MP94D2.13, MP94D2.12, MP94D2.08, MP94D2.11, MP94D2.02 and IP631-001), 5 multiple dose PK studies in healthy volunteers (MP94D2.10, MP94D4.02, IP631-001, MP94D2.13 and MP94D2.11), and 1 multiple dose PK study in patients (IP631-004). It includes two phase II PD studies (MP94D1.84 and MP94D2.01) and five phase III PD studies (MP94D2.03, MP94D2.14, MP94D4.03, IP631-003 and MP94D2.15). The sponsor investigated mass balance (MP94D2.13), metabolism (*in vitro*: Studies 51-57 and *in vivo*: MP94D2.13), relative and absolute bioavailability (MP94D2.12, MP94D2.05, and MP94D2.13), dose proportionality (MP94D2.05, IP631-001, MP94D4.02, and IP631-001) and considered the effect of drug-drug interactions (*in vitro*: Studies 51-57 and *in vivo*: IP631-004, MP94D2.11), food-drug interactions (MP94D2.07), gender (MP94D2.08, MP94D2.11, and IP631-001), ethnicity (IP631-004), age (MP94D2.08 and MP94D2.11), and renal impairment (MP94D2.02) on drug disposition.

Trospium chloride is proposed to be marketed as a sugarcoated immediate-release oral tablet in either blister packaging (blister strips; tablets) or in bottles (either 60 tablet count or 500 tablet count). The product is a brownish-yellow, glossy, sugar-coated tablet containing 20 mg of the active pharmaceutical ingredient, trospium chloride. The sponsor claims that this dosage form is identical in composition to the product currently being marketed in numerous European countries with the exception of a black printing ink being applied to US commercial supplies for identification purposes. Note that the formulation without ink was the formulation used in the pivotal clinical trials.

Because of the addition of the ink to the marketed tablet, slight processing modifications were made for the production of the US commercial supplies. The process change involves

 to the tablets. The sponsor provided bridging information (dissolution data) to support the equivalence of the tested and to-be-marketed formulations.

This NDA includes the results of a placebo-controlled study of the effect of trospium chloride on QT interval in healthy normal subjects following steady state and single oral dosing (Study #IP631-001).

Details on Select Clinical Studies

1. IP631-003

A multicenter, double-blind, placebo-controlled study of 20 mg, twice-daily trospium chloride. The objective of this study was to determine the effects of 20 mg of trospium chloride versus placebo, given twice daily, on overactive bladder associated with predominant urge incontinence over a 12-week treatment period.

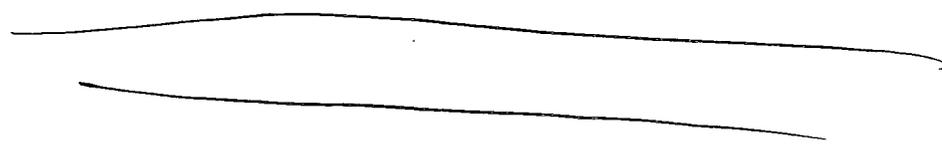
2. IP631-004

A multicenter, open-label, study in 87 patients investigating the 20 mg trospium chloride tablet dosed twice daily for up to 9 months. The objectives were to:

- Characterize the population pharmacokinetic behavior of trospium chloride in patients with overactive bladder
- Evaluate the potential effect of demographic variables, concomitant medications, and clinical pathology values on the pharmacokinetics of trospium chloride
- Assess the performance of the population pharmacokinetic model in the prediction of trospium plasma concentrations
- Characterize the relationship between systemic exposure and ECG parameters (PR and QTcF intervals and heart rate)

The sponsor provided the following:

1. Human Pharmacokinetics and Bioavailability section summary, full study report and proposed labeling
2. Drug formulation
3. Bioanalytical methods
4. *In-vitro* dissolution data
5. A list of references
6. Sponsor states that the to-be-marketed formulation of trospium chloride is equivalent to the clinical trial formulation.



Review Issues

- Dose proportionality of PK
t_{1/2}: 20 mg (18.4 hr), 40 mg (12.1 hr), 60 mg (12.5 hr)
- Change in PK parameters with chronic dosing
Multiple dose AUC (17.7) versus single dose AUC (36.4)
C_{max,steady state} (2.26) versus C_{max,single dose} (3.45)
A_{e,single dose} (4.06) versus A_{e,steady state} (2.27)
- Food effects
- Influence of renal impairment
- Drug interactions (e.g. CYP 2C9: Population PK model results versus *in vitro* results)
- Interaction with renally eliminated drugs
- Gender effects
- Chronopharmacokinetics
- Exposure-response of trospium chloride
- Effect on QT interval

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-595 is filable.

Leslie Kenna, Ph.D.

Date

Ameeta, Parekh, Ph.D., Team Leader

Date

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/s/

Leslie Kenna
6/30/03 03:08:53 PM
BIOPHARMACEUTICS

Ameeta Parekh
7/1/03 10:54:28 AM
BIOPHARMACEUTICS
I concur

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 12, 2003
TIME: 10:00 a.m.
LOCATION: 17B-43
APPLICATION: NDA 21-595/trospium chloride
TYPE OF MEETING: 45-day filing
MEETING CHAIR: Mark Hirsch, MD
MEETING RECORDER: Dale Cutright, PM

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products;
Suresh Kaul, M.D., Medical Officer, DRUDP
David Lin, Ph. D., Chemistry Team Leader, DNDC II
Jean Salemme, Ph. D., Chemist, DNDC II
Laurie McLeod-Flynn, Ph. D., Pharmacologist, DRUDP
Ameeta Parekh, Ph. D., Clinical Pharmacology Team Leader, OCPB
Leslie Kenna, Ph. D., Clinical Pharmacology Reviewer, OCPB
Mike Welch, Ph.D., Biostatistics Team Leader
Zili Li, M.D., Medical Officer, DRUDP
Jean King, R.D., Regulatory Project Manager, DRUDP
Dale Cutright, Regulatory Project Manager, DRUDP

BACKGROUND: 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. The drug substance is manufactured by _____ The drug product is manufactured by Madaus AG, Werk Troisdork in Troisdorf, Germany. Trospium chloride has already been marketed in Europe for a number of years. Because it is positively charged and does not cross the blood brain barrier, it offers the potential to cause fewer central side effects than currently approved products for this indication.

MEETING OBJECTIVES:

45-day filing meeting: to make a determination if there is sufficient material to be reviewed, adequate information to perform the review, in correct order, legible, etc.

Chemistry

- The application has all the necessary sections to review.
- The drug product manufacturing site in Germany has never been inspected.
- The stability data look adequate to support an expiry of two years.
- NDA is fileable.

Pharmacology/Toxicology

- The statistical review for the carcinogenicity studies is still outstanding. The statistician is conducting an analysis which incorporates survival data and historical data. No further data has as yet been requested from the sponsor.

- A new human pK study is underway with results expected at the 120 day safety update. It is not know what effect, if any, new human pK data will have on analysis of Pharm/Tox data.
- The proposed labeling section of the NDA did not contain information about multiples of human exposure (AUC or body surface area) in the reproductive toxicology section.
- NDA is fileable.

Clinical Pharmacology/Biopharmaceutics

- 20 of the studies presented address issues relevant to the Human Pharmacology & Bioavailability section.
- Sponsor investigated mass balance, bioavailability, dose proportionality, considered drug-drug interactions, food-drug interactions, gender, ethnicity, chronopharmacokinetics, age and renal impairment.
- The majority of radiolabeled drug was recovered in the urine. 80% of the drug eliminated in the urine is excreted unchanged.
- Of the 20% metabolized: half appears to be the product of an esterase, half unknown
- Sponsor conducting a mass balance study using [¹⁴C]-trospium chloride to verify the metabolite profile.
- Sponsor will present results of the [¹⁴C]-trospium chloride study in the 120-day safety update
- NDA is fileable.

Clinical

- The difference in one of the two co-primary endpoints appears to be small among the two treatment groups. Statistical reviewer needs to look at the p-value calculated by the sponsor.
- There is concern over slightly higher percentage of subjects in trospium groups, who developed urinary retention and chest pain.
- We need to know the number of subjects exposed to the medication for six months or longer.
- This drug has minor clinical effect, but to those patients treated, some effect is good.
- Question to determine why one of the studies was terminated.
- Proposed sites for DSI auditing: Site _____
- NDA is fileable.

Action Items

- Team members will e-mail to PM and a copy to team leader any comments (cut and paste format) to be forward to sponsor in 74-day filing letter, (July 11).
- Team members will also e-mail to PM any their notes of meeting minutes.
- The PM will telephone the sponsor and obtain a trade name, or available date, and forward the tradename consult to DMETS for review.
- The PM will forward the package insert to DDMAC for review.
- The PM will forward the request for clinical inspections to DSI, Roy Blay, Site . _____
- The consult for DCRDP has been requested, May 12, 2003.

Cc:

HFD-580/Division Files

HFD-580/Original NDA 21-595

HFD-580/Cutright/Hirsch/Kaul/Lin/Salemme/McLeod/Parekh/Kenna/Welch/Li/King

Created by: Dale Cutright, 6.12.03

Revised by: Dcutright 6/26/03

Concurrence:7/9/03

Finalized: 7/9/03 DFS

Filename:C:\Data\MyDocuments\aNDA\N21595\Mtg Min

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/s/

Dale Cutright
7/10/03 01:49:28 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-595

S-6-03

Indevus Pharmaceuticals, Inc.
Attention: Bobby W. Sandage, Jr., PhD
Executive Vice President
Research and Development
99 Hayden Ave., Suite 200
Lexington, MA 02421

Dear Dr. Sandage:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Trospium Chloride 20mg tablets

Review Priority Classification: Standard (S)

Date of Application: April 28, 2003

Date of Receipt: April 29, 2003

Our Reference Number: NDA 21-595

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 27, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 27, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-525

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jean King, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret M. 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
5/6/03 04:04:05 PM
Chief, Project Management Staff

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.

/S/

Dale Cutright
Regulatory Project Manager

/S/

Mark Hirsch, M.D.
Team Leader

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/s/

Mark S. Hirsch
5/25/04 08:14:27 AM

NDA FILEABILITY CHECKLIST

NDA Number: 21-595

Applicant: Indevus Pharmaceuticals

Stamp Date: 1-May-2003

Drug Name: Trospium Chloride 20 mg tablets

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes X

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		T-con held with sponsor May 2003 confirmed sites are ready
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	Full dissolution profiles of primary stability batches were requested during a pre-NDA CMC t-con. The profiles will be requested again in the 74-day letter.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	N/A

J. Salemme, Ph. D., Review Chemist
For Reproductive and Urologic Drug Products, HFD-580

Date: 12-June-2003

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/s/

Jean Salemmme
7/8/03 05:01:06 PM
CHEMIST

David T. Lin
7/8/03 05:13:05 PM
CHEMIST
I concur.

Teleconference Meeting Minutes

Date: April 15, 2003 **Time:** 2:00 – 2:30PM

IND: 61,381 **Drug Name:** Trospium Chloride

Indication: Treatment of Overactive Bladder (OAB)

Sponsor: Indevus Pharmaceuticals, Inc.

FDA Attendees:

Meeting Chair: David Lin, Ph.D., Chemistry Team Leader

Meeting Recorder: Jean King, M.S., R.D., Project Manager

Jean Salemme, Ph.D., Chemistry Reviewer

Sponsor Attendees:

Gregory Lerch, VP Regulatory Affairs and Pharmaceutical Development

Gwyn Reis, Senior Director Regulatory Affairs

Bobby W. Sandage, Jr., Ph.D., Executive VP Research and Development

Background: During the December 9, 2002 Pre-NDA meeting for trospium chloride, it was agreed that a teleconference would be scheduled to discuss chemistry, control, and manufacturing (CMC) issues for the sponsor anticipated NDA submission. April 3, 2003, the sponsor submitted an outline of the stability program and requested a teleconference with the Division's Chemistry Reviewer.

Sponsor's Question to FDA:

Reference is made to your question to FDA, as found in section 1.0 of the CMC Information Package of this amendment (serial #041). Herein we re-state your question and provide the Division's response.

1. Indevus considers the addition of the printing ink and slight modification of the _____ process to accomplish the printing as process modifications that should not affect the long-term stability of the product. This is supported by the fact that the stability evaluations through _____ months for printed and unprinted product are virtually identical in all packaging configurations. Therefore, we believe that the _____ month stability for the unprinted tablet and the _____ month stability for the printed tablet adequately characterize the stability of the proposed marketed product for an NDA filing. Does the Agency concur?

Division Response: The Agency cannot concur at this time whether the proposed stability data is adequate to characterize the stability of the proposed marketed product. We can concur that the proposed data package is adequate for NDA filing and review. Stability conclusions can only be determined after the data have been reviewed. We recommend that the stability data on both the printed and unprinted tablets be updated

during the review cycle. However, the data should be submitted no later than seven months from the NDA submission.

General Comments:

- The stability data presented show dissolution data were obtained at one time point. Full dissolution profiles obtained at release and during stability should be provided in the NDA. The dissolution acceptance criterion at release and/or during stability is determined during the NDA after a review of the complete dissolution profiles of the tablets. See the Biopharmaceutics Guidance to Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, and SUPAC-IR – Scale-up and Post-Approval Changes to Immediate Release Solid Oral Dosage Forms.
- The tablets to be tested in the US, and later marketed in the US, will be printed with the ink. The sponsor should provide dissolution data to demonstrate that the printed tablets are equivalent to the tablets that are not printed. If the dissolution data demonstrate the printed tablets are equivalent to the tablets that are not printed, then the stability data, including the dissolution data, generated for the unprinted tablets can be used as supplemental stability data for the printed tablets.
- See ICH Q1E for our current thinking on extrapolation of stability data to grant an expiration dating period.
- We note that two types of PVC blisters will be used for the to-be-marketed product. Anticipating that you will have limited data for the PVC Aclar blister but more data for the PVC blister, you should demonstrate that the blister made with PVC Aclar is as effective at protecting the quality of the drug product as the blister made with PVC.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

David T. Lin
5/12/03 06:19:51 PM
I concur.

Meeting Minutes

Date: December 9, 2002 **Time:** 10:30 AM to 12:00 PM

Location: Potomac Room, Parklawn Bldg.

IND: 61,381 **Indication:** Treatment of Overactive Bladder (OAB)

Drug Name: Trospium Chloride

Sponsor: Indevus Pharmaceuticals, Inc. **Type of Meeting:** Pre-NDA Type B Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Jean King, M.S., R.D.

FDA Attendees:

Mark Hirsch, M.D., Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP,HFD-580)

Brenda Gierhart, M.D., Medical Officer, (DRUDP,HFD-580)

Venkateswa Jarugula, Ph.D., Pharmacokinetic Reviewer, (DRUDP,HFD-580)

Mike Welch, Ph.D., Biostatistics Team Leader, (DRUDP,HFD-580)

Jean King, M.S., R.D., Project Manager, (DRUDP,HFD-580)

Laurie McLeod, Ph.D., Toxicology Reviewer, (DRUDP,HFD-580)

Marcea Whitaker, M.D., Medical Officer, (DRUDP,HFD-580)

Audrey Gassman, M.D., Medical Officer, (DRUDP,HFD-580)

Max Koppel, M.D., Medical Officer, (DRUDP,HFD-580)

Sponsor Attendees:

Gregory Lerch, VP Regulatory Affairs and Pharmaceutical Development

Gwyn Reis, Senior Director Regulatory Affairs

LuAnn Sabounjian, Executive Director Clinical Research

Bobby W. Sandage, Jr., Ph.D., Executive VP Research and Development

Ute Schwiderski, Ph.D., VP Biostatistics and Data Management

Mark Eller, PhD, Vice President, Clinical Pharmacology

Kim Frieze, Medical Writing Scientist, RTS

Sue Garnett, Senior Director, Regulatory & Technical Services

Tamara Pinkett, Senior Biostatistician

Debbie Tady, Medical Writing Scientist, RTS

Meeting Objective: The specific objectives, as proposed by Indevus, were:

1. Provide a concise overview of the current status of the trospium chloride development program.
2. Reach agreement with the FDA regarding the proposed content of the trospium chloride NDA.
3. Address specific questions regarding the clinical section of the trospium chloride NDA planned for submission in April 2003.

Discussion/Decisions Made:

A: FORMAT AND CONTENT OF THE INTEGRATED SUMMARY OF SAFETY (ISS):

Question # 1. Are the outlined Indevus plans for the format and content of the Integrated Summary of Safety (ISS) acceptable to the Division?

FDA Response:

The Division acknowledged that the proposed format and content of the ISS was acceptable. Additionally, the Division recommended that the ISS contain a discussion (with supporting tabular data) of the differences between non-US and US safety results.

The Division questioned how much long-term safety data would be included in the original NDA. Indevus responded that safety information on more than 300 patients treated for 6 months, and more than 200 patients treated for one year or longer, will be included in the NDA. The Safety Update will include information on 350 patients treated for 6 months, but will not include any more information on patients treated for one year.

The Division stated that the plan for patient narratives was acceptable because case report forms will be available. Indevus responded that there are some patients for whom case report forms are not available from some of the open-label studies. The Division responded that this also should be explained in the ISS.

Indevus asked whether it is acceptable that by-patient listings not be included in the NDA. Because information for each patient will be accessible in the NDA by way of data sets and by-domain listings, the Division agreed that by-patient listings are not required.

B: FORMAT AND CONTENT OF THE INTEGRATED SUMMARY OF EFFICACY (ISE):

Question # 2. Are the outlined Indevus plans for the format and content of the Integrated Summary of Efficacy (ISE) acceptable to the Division?

FDA Response:

As with the ISS, the Division agreed that the proposed format and content of the ISE was acceptable. However, the Division recommended the inclusion of a discussion comparing European and US efficacy results (i.e., diary data). Information regarding the urodynamic data from Europe can be included as a separate discussion.

The Division noted that the NDA will be composed of the Phase III US trial and supportive evidence from the European trials, including Studies MPD2.04 and MP94D2.15 with one large US study and supportive European data, the NDA is probably filable.

In an additional discussion regarding efficacy analyses and claims, the Division had the following comments about Study MP94D2.04:

1. The dose of Ditropan (5mg bid) given was the minimal effective dose for the drug.
2. The sample size for the comparator-drug arm was small and there was no placebo arm.
3. The primary efficacy endpoints were urodynamic endpoints, not diary data.
4. The diaries used were 2-day diaries, while the current standard is 7-day diaries. The 2-day diaries could be acceptable, however, if it is shown that they were complete.
5. It is not clear if the time-points or endpoints of interest were predefined.
6. It is not clear if the population enrolled is exactly the same as the currently defined OAB population.
7. Time intervals in which incontinence episodes occurred are presented rather than actual numbers of episodes.
8. This study is, on its face, insufficient to support a comparative claim in labeling of any sort.
9. The study protocol was not reviewed by the Division prior to trial conduct.

The Division also considers Study MP94D2.15 to be supportive and had the following comments with regard to its design/results:

1. The study included only a 3-week treatment period.
2. It is not clear if the population enrolled is exactly the same as the currently defined OAB population.
3. The trial had a relatively small sample size in each of the treatment arms.
4. The change-from-baseline results for number of micturitions and incontinence episodes were not statistically significant when ITT samples were used for analysis.
5. The study protocol was not reviewed by the Division prior to trial conduct.

Additional Statistical Analyses Issues: In additional statistical discussions, the Division questioned the intended meaning of “additional analyses” in reference to the European studies. Indevus responded that the protocol for Study MP94D2.04 did not provide for inferential statistics to be performed on the diary data collected, therefore analyses based on the methods employed in the Ditropan XL NDA (as represented in the SBA) were retrospectively applied by Indevus. Similarly, since inferential statistics were not specified for the volume-voided data collected in Study MP94D2.15, Indevus analyzed those data as well. In addition, the micturition-frequency and incontinence-episode data from MP94D2.15 were reanalyzed to gain a better understanding of the results presented in the original study report. The Clinical Study Reports for these trials, which will be provided in the NDA, were prepared by the studies sponsor, Madaus, and do not contain results from the additional analyses. Rather, results from the analyses performed by Indevus will appear in the ISE. The Division requested that this also be explained in the ISE.

The Division also requested that efficacy analyses stratified by baseline frequency be provided for Study IP631-003. Also, efficacy results should be analyzed across sites and urge incontinence results should be displayed in both terms of change-per-week and change-per-day. Lastly, all variable names for SAS transport files should not be more than eight characters in length.

The Division commented that results for 1) nocturnal toilet voids, 2) percent patients cured of incontinence, 3) urgency severity and 4) onset of action will be examined during the NDA review to determine what, if anything, can be stated in the labeling about these endpoints. The Division also commented that the urgency scale employed has not been validated.

Indevus replied that it would evaluate the feasibility of using information collected in Study IP631-003 to validate the urgency severity scale. Indevus then inquired what would be required

to make labeling claims for the secondary endpoints, specifically whether another trial evaluating these same parameters would be needed. The Division will review this request and relay a response to Indevus at a later date.

C: CLINICAL PHARMACOLOGY

Question # 3. Indevus proposes to submit the NDA without a hepatic impairment PK study, but will evaluate data from the two ongoing trials to assess the need for conducting such a study post-NDA. Is this approach acceptable to the Division?

FDA Response:

The Division remarked that since the drug is minimally metabolized and has minimal potential for drug-drug interactions, the NDA is filable without a study in patients with liver impairment. However, the draft guidance recommends such a study if a drug is greater than 20% metabolized. It is not clear, from the data collected thus far, the exact extent of metabolism for trospium. From the IV mass balance study it is known that 56% of the administered dose is excreted unchanged in the urine, but there is no information about the feces. Thus, the lack of a hepatic-impairment study may become a review issue.

Indevus explained that population pharmacokinetics are being analyzed in the open-label portion of Study IP631-003 and that liver function test values will be examined as covariates. Indevus asked if that type of information would suffice in lieu of a hepatic impairment study. The Division responded that unless there were patients with widely varying degrees of liver function enrolled in the study, information obtained from this analysis would be insufficient.

In an additional discussion, the Division asked that the following be done in the clinical pharmacology section of the NDA:

1. Identify all major metabolites and characterize the metabolic pathway for each.
2. Determine the pharmacological activity of all major metabolites
3. Determine enzymes responsible for the metabolism of trospium.
4. Discuss the role of CYP 450 in the metabolism of trospium.
5. Clarify what isozymes were included in the in vitro tests – it is not clear whether 2C9 was included and it should have been.
6. Discuss the potential for interactions with drugs that could alter the renal excretion of trospium.
7. Explain how trospium was given in relation to meals in the clinical trials and make an appropriate labeling recommendation given the fact that food intake reduces the bioavailability of the drug by up to 80%.

To this statement, Indevus explained that the drug was given one hour before meals in Study IP631-003 and that the draft labeling recommends giving the drug on an empty stomach. The Division commented that Indevus give consideration to more exact wording for the labeling and that the Division would later review the sponsor's assessment.

8. Recommend an appropriate dosage adjustment in patients with renal impairment. The Division commented that the current draft label recommends once-daily or once every-other-day dosing for renally-impaired patients. The Division recommended that the dose given to patients with renal impairment should be reduced, rather than altering the dose interval.

To this comment, Indevus stated that a simulation had been done to estimate C_{max} in patients with renal impairment and asked if the Agency would find information from the simulation helpful. The Division responded that it had serious reservations about relying upon simulated data. Unless the results were overwhelmingly convincing, information from the simulation would not be sufficient.

9. Discuss any dose-response data in Sections 6 and 8.3.

Indevus explained that there were dose-response data for urodynamic measures at doses of 10, 20 and 40 mg, bid.

10. Include the QT study (IP631-001) results in the clinical pharmacology section as well as in Section 8.

D: PEDIATRIC RULE

Question # 4. Indevus plans to submit with the pre-NDA meeting package a partial waiver for conducting trials in very young children and a request for deferral of the requirements for conducting clinical trials in older children. **Does the Division have any further guidance on this plan in light of recent court cases?**

FDA Response: Currently, the Agency is unable to grant a waiver or deferral of Pediatric Rule requirements since the US District Court decision on October 17, 2002 enjoined the FDA to not enforce the Pediatric Rule. However, the Agency encourages continued studying of drugs in pediatric patients so that appropriate use information can be labeled.

E: NONCLINICAL QUESTIONS (INCLUDING ELECTRONIC FORMAT QUESTION FOR ENTIRE NDA)

Question # 1. We believe that the enclosed information adequately addresses CAC's concerns. **Does the Division concur?**

Response: No. The re-reading of the lung neoplasm slides was acceptable, as were the historical data for that tissue. Those data have been forwarded to the statistician along with CAC's comments. His analysis will incorporate survival data, due to the low rate of survival in some groups and the presence of tumors in those groups. There may be positive trends for neoplasms other than in the lung, and we are requesting historical data for those tissues as well, as mentioned in the Executive CAC minutes of 1 May 2001. Those historical data should be from studies of the same duration as the corresponding carcinogenicity study and from approximately the same period (± 5 years). They should be submitted in the format shown in the guidance. The guidance also describes how study data should be formatted and how time of death for each animal should be included in the table.

Question # 2. References corresponding to each technical summary will be grouped and appear at the end of the section. Is this approach (to data organization) acceptable to the Division?

Response: Yes. The format is acceptable. It is not specifically mentioned that line listings of the original raw individual animal data will be included. Please include those data.

Question # 3. Does the Agency concur that the proposed literature-review strategy is adequate?

Response: Yes

Question # 4. Please confirm that electronic submission with paper copy of volume I is acceptable.

Response: Please refer to the Guidance for Industry: Providing Regulatory Submissions in Electronic Format-General Considerations dated January 1999 for guidance regarding submitting the NDA archival copy. This Guidance (on page 15) states that it is acceptable for the archival copy of an electronic submission to only be accompanied with a paper copy of the cover letter for the submission, a paper copy of the appropriate FDA form for the submission (i.e. FDA form 356h), and the electronic media for archiving.

You are referred to the Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs dated January 1999 for guidance regarding submitting the NDA review copies. The Guidance (on page 5) states that if you provide the archival copy in electronic format, you only need to provide a portion of the review copy in paper.

Please note that the above NDA submission guidance does not address the field copy of the chemistry section of the NDA submission for the good manufacturing practice inspections by the district offices.

It would be greatly appreciated if eight paper copies of Volume 1 were submitted: one copy for the document room, one copy for the project manager, one copy for each of the five reviewers (i.e. Clinical, Clinical Pharmacology and Biopharmaceutics, Pharmacology, Chemistry, and Biometrics), and one copy for DSI. In addition, DSI would appreciate receiving a hard copy of the Phase 3 Protocol IP631-003; a hard copy of all amendments to Protocol IP631-003; a listing to include the names and addresses of the IP631-003 investigators; the number of subjects enrolled at each site; the number of subjects at each site who discontinued due to adverse events; the number of subjects at each site who completed the trial; and the number of Serious Adverse Events at each site. Another option would be to create a specific folder in the electronic submission (labeled "DSI") containing high level links for DSI to the requested information.

F: Financial Disclosure Statements: The Division informed Indevus that financial disclosure statements must be submitted with the NDA and requested submission of a summary for the Phase III trial investigators, optimally prior to the NDA submission. The Division provided Indevus with an outline for submitting financial disclosure information, which should be broken out by center with the number of subjects enrolled at each center included. If a study is to be considered "pivotal", financial disclosure information for the trial is also required.

G: CMC Submission: In their packet submission for this meeting, Indevus noted that they had not included information or questions regarding the Chemistry, Manufacturing and Controls section of the NDA, but would like to schedule a future meeting to discuss the CMC section of the NDA.

FDA Response: The Division agreed that that a teleconference should be scheduled to address the CMC issues in this NDA submission.

Action Items:

1. The sponsor will clarify in the ISS section of the NDA that there are some patients for whom case report forms are not available from some of the open-label studies.

2. If a non-sedating claim is sought by the sponsor with supportive data included in the NDA to demonstrate the drug's lack of CNS effects, the Division will consult with the Division of Neuropharmacological Drug Products regarding appropriate sleepiness scales.
3. The sponsor will clarify the intended meaning of "additional analysis" in reference to the European studies in the ISE section of the submitted NDA.
4. The sponsor will stratify the efficacy analyses by baseline frequency for Study IP631-003. Also, the sponsor will analyze the efficacy results across sites and urge incontinence results will be displayed in both terms of change-per-week and change-per-day. Lastly, the sponsor will ensure that all variable names for SAS transport files are not more than eight characters in length.
5. The sponsor will review the information collected in Study IP631-003 to determine if it is sufficient to validate the urgency severity scale.
6. The Division will take under consideration the sponsor's inquiry regarding the necessity to conduct a separate trial to support labeling claims for the secondary endpoints.
7. The sponsor will consider incorporating the recommendations into the clinical pharmacology section of the NDA:
 - Identify all major metabolites and characterize the metabolic pathway for each.
 - Discuss the pharmacological activity of the metabolites.
 - Identify enzymes responsible for the metabolism of trospium.
 - Discuss the role of CYP 450 in the metabolism of trospium as defined in the planned ¹⁴C study.
 - Clarify what isozymes were included in the in vitro tests – it is not clear whether 2C9 was included and it should have been.
 - Discuss the potential for interactions with drugs that could alter the renal excretion of trospium.
 - Explain how trospium was given in relation to meals in the clinical trials and make an appropriate labeling recommendation given the fact that food intake reduces the bioavailability of the drug by up to 80%.
 - Recommend an appropriate dosage adjustment in patients with renal impairment.
 - Discuss any dose-response data in Sections 6 and 8.3.
 - Include the QT study (IP631-001) results in the clinical pharmacology section as well as in Section 8.
8. Because of the possibility of positive trends for neoplasms other than in the lung, the sponsor will submit historical data from studies of the same duration as the corresponding carcinogenicity study and from approximately the same period (\pm 5 years), using format shown in the guidance.
9. The sponsor will include in the NDA line listings of the original raw individual animal data.
10. The sponsor will refer to the Guidance for Industry: Providing Regulatory Submissions in Electronic Format-General Considerations dated January 1999 for guidance regarding submitting the NDA archival copy and the Guidance for Industry:

Providing Regulatory Submissions in Electronic Format-NDAs dated January 1999 for guidance regarding submitting the NDA review copies.

11. The sponsor will consider submitting eight paper copies of Volume 1.
12. The sponsor will consider submitting for a DSI consult the following items: a hard copy of the Phase 3 Protocol IP631-003; a hard copy of all amendments to Protocol IP631-003; a listing to include the names and addresses of the IP631-003 investigators; the number of subjects enrolled at each site; the number of subjects at each site who discontinued due to adverse events; the number of subjects at each site who completed the trial; and the number of Serious Adverse Events at each site. Another option would be to create a specific folder in the electronic submission (labeled "DSI") containing high level links for DSI to the requested information.
13. Optimally, prior to the NDA submission, the sponsor will submit the appropriate financial disclosure statements, a summary for the Phase III trial investigators, and if applicable, financial disclosure information for any "pivotal" trial
14. The Division will schedule a teleconference with the sponsor to discuss the CMC issues in this NDA submission.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Mark S. Hirsch
1/9/03 04:39:11 PM
I concur.

Meeting Minutes

Date: May 22, 2000 **Time:** 3:30-4:45 PM EST **Location:** Parklawn; Conf. Rm. C

Pre-IND **Drug:** Trospium **Indication:** urinary incontinence

Sponsor: Interneuron Pharmaceuticals, Inc.

Type of Meeting: Guidance

Meeting Chair: Marianne Mann, MD – Deputy Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

Meeting Recorder: Evelyn R. Farinas, RPh, M.G.A. – Regulatory Project Manager

FDA Attendees:

Marianne Mann, MD – Deputy Director, DRUDP (HFD-580)

Daniel Shames, MD – Medical Team Leader, DRUDP (HFD-580)

George Benson, MD – Medical Officer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Venkateswar Jarugula, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Alexander Jordan, Ph.D. – Pharmacology Team Leader, DRUDP (HFD-580)

Kate Meaker, M.S. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Evelyn R. Farinas, RPh, M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:

Sonja Barton Loar, Pharm. D. – Vice President Regulatory and Scientific Affairs

Bobby W. Sandage, Jr., Ph.D. – Executive Vice President of Research and Development

Kenneth Locke, Ph.D. - Executive Director, Preclinical Development

Gregory Lerch – Executive Director, Regulatory Affairs and Pharmaceutical Development

LuAnn Sabounjian, BSN – Director, Clinical Research

Ute Schwiderski, Ph.D. – Executive Director, Biostatistics and Data Management

Lisa Wood, RA-C – Regulatory Affairs Coordinator

_____ Consultant for Interneuron Pharmaceuticals, Inc.

Michael Schaefer – Head of Research and Development, Madaus AG, Cologne

Monika Grosse-Freese – Medical Advisor, Madaus AG, Cologne

Meeting Objective: To provide guidance to the sponsor regarding future development program of trospium chloride.

Background: Interneuron Pharmaceuticals, Inc. has licensed trospium chloride from Madaus AG as an anticholinergic agent for the treatment of patients with overactive bladder. Trospium chloride has been approved for marketing in several European countries. In correspondence dated March 23, 2000, the sponsor provided background material for the

Pediatric Rule:

- sponsor may be required to conduct pediatric studies if there is a potential for use in pediatric subjects (up to —years of age); sponsor may ask for a waiver or deferral, and provide the rationale for the request
- the small pediatric study proposed in the slide presentation would not satisfy the requirements of the Pediatric Rule
- the intent of the Pediatric Rule is to augment the information in the label

Toxicology:

A full program has been conducted. Several of the studies, including the 6 month rat, Segment I repro (rat), Segment II repro (rat and rabbit) were conducted *prior* to the issuance of the current GLP/ICH guidelines. In most respects, these studies are in compliance with the current guidelines. We propose to submit these studies in support of the IND/NDA regulatory filings, rather than to repeat these studies; any deviations from the current guidelines will be fully described in our filings. Do you concur with this approach?

- yes, but the sponsor should explain how the studies differed from studies done under GLP's; this is not necessary for the single dose studies

A GLP 6 month tox study in dogs was completed *prior* to the issuance of the ICH guideline for a 9 month non-rodent study. Given that the dog study was conducted according to current GLP guidelines, and given the considerable clinical experience with trospium, is it necessary to conduct a new longer-term (9 month) dog study?

- the 6-month dog study is acceptable based on the toxicity seen in the short term studies with higher doses; since higher doses probably cannot be investigated, little additional safety data would be obtained by testing similar doses for an additional three months
- the sponsor should submit carcinogenicity protocols for review by the executive Carcinogenicity Assessment Committee

Statistical:

- the following information is required in the statistical analysis plan: specific objective(s), primary endpoint(s) and time point(s), hypothesis tests, testing methods and sample size calculations
- if there are multiple primary endpoints, DRUDP suggests that the sponsor propose an adequate statistical adjustment

Biopharmaceutics:

- the rationale for dosing recommendations in severe renally impaired patients should be provided in the NDA
- a justification of the time interval required between drug administration and food consumption should be provided in the NDA
- DRUDP recommends that sponsor specify the differences between clinical trial and commercial formulations
- Pharmacokinetic/Pharmacodynamic correlations were not studied; sponsor is planning to measure drug blood levels in ECG studies and explore PK/PD relationship

Decisions reached:

- the sponsor will consider DRUDP's recommendations and guidance for IND and NDA submissions

Action Items:

- minutes will be provided to sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Pre-IND
Industry Minutes May 22, 2000
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cc:

HFD-580/ Allen/Mann/Shames/Benson/Rhee/Parekh/Kammerman/Meaker/Jordan/Rumble

drafted: Farinas, 5.26.00

concurrence: Mann 6.2.00/Shames 6.2.00/Benson 6.2.00/Rhee 6.1.00/Jordan 6.2.00/Parekh
6.09.00/Jarugula 6.2.00/Meaker 6.5.00/Rumble 6.1.00

final: Farinas, 6.09.00

MEETING MINUTES

Note: refaxed to Bobby Sandage on 2.27.01

Note: hard copy in DFS, signed by ERF and MM

/s/

Marianne Mann
3/7/01 12:55:51 PM

NDA 21-595
Sanctura

Advisory Committee Meetings

No advisory committee meeting was held for this application.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-595
Sanctura

Federal Register Notices

Not applicable for this application.

**APPEARS THIS WAY
ON ORIGINAL**

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Division Director Memo

See Group Leader's Memo

**APPEARS THIS WAY
ON ORIGINAL**