

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-028

Trade Name: Cosyntropin
Established Name: Cosyntropin
Strengths: 0.25 mg/mL for Injection
Applicant: Sandoz Inc.
Agent for Applicant: Beth Brannan, US Agent for Sandoz

Date of Application: February 3, 2006
Date of Receipt: February 6, 2006
Date clock started after UN: N/A
Date of Filing Meeting: April 6, 2006
Filing Date: April 7, 2006
Action Goal Date (optional):

User Fee Goal Date: **December 6, 2006**

Indication requested: As a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency.

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.) NO

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Not paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES
- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
If no, explain:
- If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all forms and certifications must be in paper and require a signature. – Done.
Which parts of the application were submitted in electronic format? All modules, and paper 1.1

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? YES
- Is it an electronic CTD (eCTD)? YES
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed. – Done.

Additional comments:

- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? _____ NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES
- PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. YES.
- List referenced IND numbers: 69,720
- End-of-Phase 2 Meeting? _____ NO X
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting? Date: 9/22/04 YES
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES X
- Risk Management Plan consulted to ODS/IO? N/A
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A

Chemistry

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 6, 2006

ATTENDEES: Drs. Kehoe, Lubas, Antonipillai, Davis-Bruno, Ahn, Wei, Tran, Haber, Mello, Hussong,
And Ms. Parise and Weber.

ASSIGNED REVIEWERS (including those not present at filing meeting):

| <u>Discipline</u> | <u>Reviewer</u> |
|---|--------------------------|
| Medical: | Kehoe |
| Secondary Medical: | Lubas |
| Statistical: | Sahlroot |
| Pharmacology: | Davis-Bruno/Antonipillai |
| Statistical Pharmacology: | NN |
| Chemistry: | Fraser/Tran/Haber |
| Environmental Assessment (if needed): | Haber |
| Biopharmaceutical: | Ahn/Wei |
| Microbiology, sterility: | Hussong/Mello |
| Microbiology, clinical (for antimicrobial products only): | N/A |
| DSI: | Himaya |
| Regulatory Project Management: | Weber |
| Other Consults: | DDMAC/DMETS |

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE

- Clinical site inspection needed? NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A

CLINICAL MICROBIOLOGY FILE

STATISTICS FILE

BIOPHARMACEUTICS FILE

IV soln., small peptide drug, buffer is different.

- Biopharm. inspection needed? YES (DSI)

PHARMACOLOGY FILE X

- GLP inspection needed? NO

CHEMISTRY

FILE

- Establishment(s) ready for inspection? YES
- Microbiology YES

ELECTRONIC SUBMISSION:

Any comments: paper + electronic submission.

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- 3.X Convey document filing issues/no filing issues to applicant by Day 74.

Jena Weber, PM

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES

If "No," skip to question 3.

2. Name of listed drug referenced by the applicant and NDA: **Amphastar NDA 16-750
Cortrosyn™ (cosyntropin) 0.25 mg/mL for Injection (lyophilized powder).**

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent to the product proposed in the 505(b)(2) application that is already approved?

Different dosage form (solution vs, lyophilized powder).

NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent cited as the listed drug?

(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative already approved? YES

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES

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

Same drug and indication; NDA 22-028 is a sterile solution in vials containing 0.25 mg of cosyntropin; listed NDA is a lyophilized powder for reconstitution for injection.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).

NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9).

NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9).

NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- X 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.
(Paragraph I certification)
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
YES

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?

N/A

NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 69,720

OR

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

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES

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

/s/

Jena Weber
12/12/2006 08:37:22 AM
CSO

MEMORANDUM

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

DATE: November 28, 2006

TO: Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology
Products (DMEP)

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-028, Cosyntropin
Injection, 0.25 mg/mL, Sponsored by Sandoz Canada,
Inc.

At the request of DMEP, the Division of Scientific
Investigations (DSI) audited the clinical and analytical
portions of the following bioequivalence study, performed at

b(4)

Study# 50525: "Randomized, Open-Label, 2-Way Crossover,
Bioequivalence, Pharmacodynamic Endpoint Study
of Cosyntropin 0.25 mg/mL Injection and
Cortrosyn (Reference) Following a 0.25 mg
Intravenous Dose in Healthy Subjects"

Following the inspection at _____ no Form
FDA-483 was issued, and no significant clinical and analytical
observations were found concerning Study 50525.

b(4)

Conclusion:

DSI recommends that the clinical and analytical data from Study 50525 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Martin K. Yau, Ph.D.
Pharmacologist

Final Classification:

b(4)

APPEARS THIS WAY
ON ORIGINAL

CC:

HFD-45/RF

HFD-48/Yau/Himaya/CF

OND/ODEII/DMEP/Weber/NDA 22-028

OTS/OCF/DCP2/Wei

HFR-NE200/

Drafted: MKY 11/28/06

DSI:5696; O:\BE\EIRCover\22028ana.cos.doc

FACTS: 742342

b(4)

Please complete these brief notes for each EIR covering memo:

Application No: N22-028 (DSI# 5696)

Drug name: Cosyntropin Injection, 0.25 mg/mL

Reviewing Division: Division of Metabolism and Endocrinology Products

Review Completion Date: 11/28/06

| Site # | Firm Name, US State or Foreign Country | Type: An/Cl | Recommendation | HQ Class |
|--------|--|-------------|--|----------|
| 1 | _____ | An | Recommends the clinical and analytical data from Study 50525 be Accepted for Review. | NAI |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |

b(4)

| Site # | | | | Deficiencies | Description |
|--------|---|---|---|--------------|--|
| 1 | 2 | 3 | 4 | | |
| x | | | | NA | No Form FDA-483 was issued following the audit at _____ |
| | | | | | |

b(4)

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420**

FROM: **DEMP**
Jena Weber, PM

| | | | | |
|---|---------|------------------------------------|---|---|
| DATE: 12/11/06 | IND NO. | NDA NO. 22-028 | TYPE OF DOCUMENT Response to DMETS consult | DATE OF DOCUMENT 12/4/06 |
| NAME OF DRUG: Cosyntropin Injection 0.25 mg/mL | | PRIORITY CONSIDERATION S | CLASSIFICATION OF DRUG: Diagnostic agent to screen for adrenocortical insufficiency | DESIRED COMPLETION DATE January 15,2007 |

NAME OF FIRM: **Sandoz Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Sandoz response to DMETS recommendations; FDA letter issued 11/3/06.**

PDUFA DATE: 12/6/06; AE letter issued.

ATTACHMENTS: See electronic submission in EDR dated 12/4/06.

NAME AND PHONE NUMBER OF REQUESTER

Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

Jena Weber
12/11/2006 01:53:56 PM

Weber, Jena M

From: Wei, Xiaoxiong
Sent: Monday, November 27, 2006 2:19 PM
To: CDER-OCPB
Cc: Lubas, William (CDER); Weber, Jena M
Subject: Optional Intra-Division Level CP Briefing for NDA22-028 Cosyntropin
Attachments: NDA22-028 Cosyntropin injection-020306.doc; N22-028 Label-clear.pdf

An Optional Intra-Division Level CP Briefing has been scheduled for NDA22-028 Cosyntropin with the following details:

Date: Dec. 1, 2006 (Friday)
Time: 11:30 AM – 12:30 PM
Where: Bldg 21, Conf room 4560

NDA: 22-028
Drug Name: Cosyntropin
Sponsor: Sandoz Canada, Inc.
Reviewer: Jim Wei
Team Leader: Hae-Young Ahn
OCP Division: Division of Clinical Pharmacology 2
OND Division: Division of Metabolic and Endocrine Products
Formulation: 0.25 mg solution
Dosing regimen: Diagnostic agent, 0.25 mg IV
Indication: Screening of adrenocortical insufficiency

This is a 505 (b) (2) application to seek marketing of Cosyntropin, a synthetic partial sequence (α 1-24 amino acids) of ACTH. The reference drug product is Amphastar's synthetic cosyntropin, Cortrosyn, which was approved in 1970 under NDA16-750. Based on an agreement with the Agency, there is no requirement for the pharmacokinetic data to demonstrate bioequivalence because of the route of intravenous administration.

Cosyntropin exhibits the full corticosteroidogenic activity of natural ACTH. It has been established that 0.25 mg of cosyntropin will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. Cosyntropin injection is intended for use as a diagnostic agent in the screening of patients with adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex it has been utilized to perform a 30-minute test of adrenal function in most cases.

To support this 505 (b) (2) application, the sponsor conducted a single center, randomized, single-dose, open-label, 2-way crossover bioequivalence study. The sponsor compared the plasma cortisol concentration response, a pharmacodynamic marker, of a test drug product cosyntropin versus Cortrosyn, a reference cosyntropin, under fasting conditions. A single dose of cosyntropin as a 1 mL x 0.25 mg/mL injection was administered intravenously in each study period. The treatment phases were separated by a washout period of 5 days. The sponsor used both baseline corrected and uncorrected data for BE analysis. The results using baseline corrected data showed that AUC_{0-inf} and C_{max} passed the BE acceptance criterion. However, the 90% confidence interval for AUC_{0-t} was a little off the upper bound limit as 126.47%. In conclusion, the cortisol response is comparable between the test cosyntropin (treatment A) and the reference Cortrosyn (Treatment B) following 0.25 mg intravenous dose.

The review and draft PI are attached for your reference.

Regards,

Jim

APPEARS THIS WAY
ON ORIGINAL

11/28/2006

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; White Oak BLDG 22, Room 4447
Center for Drug Evaluation and Research

To: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products, HFD-510

Through: Nora Roselle, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

From: Linda Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: October 17, 2006

Subject: OSE Review #: 2006-479; Cosyntropin Injection (0.25 mg/mL): NDA# 22-028

11/2/06

This memorandum was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for an assessment of the revised labels and labeling for Cosyntropin Injection submitted on September 21, 2006. These revisions were provided in response to DMETS comments dated February 3, 2006. We note that the sponsor has addressed all of our concerns identified in the DMETS review. However, we have identified the following additional concerns with respect to the revised labels and labeling:

DMETS notes that the sponsor has included a warning that includes the statement "*For Intravenous Use Only*". This statement is qualified on the carton labeling with an asterisk that identifies the statement "*Not to be administered by the intramuscular route*". However, this statement does not appear on the container label. DMETS recommends that this information also be included on the container label, if space permits.

Revised
11/3/06

Despite the sponsor's improved differentiation of this product from Cortrosyn, DMETS continues to encourage the sponsor to institute an education campaign to inform practitioners of the differences between these two products.

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 Diane Smith, Project Manager, at 301-796-0538.

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this page is the manifestation of the electronic signature.**

/s/

Linda Wisniewski
11/2/2006 03:27:29 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/2/2006 03:30:58 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/2/2006 03:47:00 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420**

FROM: DEMP
Jena Weber, PM

DATE: 10/5/06

IND NO.

NDA NO.
22-028

TYPE OF DOCUMENT
Response to DMETS
consult

DATE OF DOCUMENT
9/21/06

NAME OF DRUG: Cosyntropin
Injection 0.25 mg/mL

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG:
Diagnostic agent to screen
for adrenocortical
insufficiency

DESIRED COMPLETION DATE
November 15, 2006

NAME OF FIRM: Sandoz Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Sandoz response to DMETS recommendations; FDA letter send 8/14/06.

PDUFA DATE: 12/6/06

ATTACHMENTS: See electronic submission in EDR dated 9/21/06.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)

DFS ONLY MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Jena Weber

10/5/2006 05:59:52 AM

Weber, Jena-M

From: Lubas, William (CDER)
To: Thursday, September 28, 2006 11:23 AM
Kehoe, Theresa
Cc: Weber, Jena M
Subject: Cosyntropin Medical Review

Attachments: Cosyntropin Med Rev 505b2 final.dot

Hi Theresa,
Here is my draft review for Cosyntropin.



Cosyntropin Med
Rev 505b2 fina...

I don't have a problem with this from a medical point of view and just plan to suggest that they get more pediatric data and watch out for the potential of increased immunogenicity as part of a nonbinding post marketing commitment. Therefore, I would give them a full pediatric waiver for this indication using the reason that "Products in this class and for this indication have been studied/labeled for pediatric population" My 1996 Harriet Lane did not have any dosing information for Cosyntropin, and the library did not have a newer version. A Pediatric Endocrinology book I found in the library recommended a dose of 250mcg for all pediatric patients. The Pediatric Dosing Handbook recommended 250mcg for kids over 2 and 125 for kids under 2 and 15mcg/kg for neonates. I included this information in my review.

At the end of section 4.4 Data Quality and Integrity in red to remind to check on the final results of the study audit, which is still pending.

As far as I know chemistry was still working on this submission so I don't know if they will have any outstanding issues.

I incorporated the DMETS comments into my review and included most of them in section 9.5 Comments to Applicant, but I think we can probably resolve them during labeling negotiations. As far as I know we have not heard back from the sponsor with the long list of questions DMETS had for them.

Let me know if you have any comments.

Regards,
Bill

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(WO: 22, Mailstop 4447)

| | | |
|--|---|------------------------------|
| DATE RECEIVED: April 17, 2006 DATE OF DOCUMENT: February 3, 2006 | DESIRED COMPLETION DATE: September 1, 2006 PDUFA DATE: December 6, 2006 | OSE REVIEW #: 06-0116 |
|--|---|------------------------------|

TO: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
HFD-510

THROUGH: Alina Mahmud, RPh., MS, Team Leader
Denise Toyer, PharmD., Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Cosyntropin Injection
0.25 mg/mL

NDA# : 22-028

NDA SPONSOR: Sandoz, Inc.

RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in section II of this review in order to minimize potential errors with the use of this product.

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 Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO: 22; Mailstop: 4447
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: May 1, 2006
NDA#: 22-028
NAME OF DRUG: Cosyntropin Injection
0.25 mg/mL
NDA HOLDER: Sandoz, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Product (HFD-510), for assessment of the labels and labeling for Cosyntropin Injection. This is a 505(b)(2) application and the reference listed drug for this product is Cortrosyn, which is administered intramuscularly and intravenously (NDA# 16-750). DMETS notes that the sponsor did not submit a proprietary name for this product.

PRODUCT INFORMATION

Cosyntropin Injection is indicated for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. Cosyntropin Injection may be administered as a direct intravenous injection when used as a rapid screening test of adrenal function. It may also be given as an intravenous infusion over a 4 to 8 hour period to provide a greater stimulus to the adrenal glands. Doses of Cosyntropin injection 0.25 mg to 0.75 mg have been used in clinical studies and a maximal response noted with the smallest dose. Two alternative methods of administration are intravenous injection and infusion. Cosyntropin injection can be injected intravenously in 2 to 5 mL of saline over a 2 minute period. When given as an intravenous infusion: cosyntropin injection, 0.25 mg/mL may be added to glucose or saline solutions and given at the rate of approximately 40 micrograms per hour over a 6 hour period. It is supplied in vials containing 0.25 mg/mL and is packaged in boxes of 10 vials.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

sent 4/14/06

In the review of the container labels, carton and insert labeling of Cosyntropin Injection, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. DMETS has concerns about the potential interchanging of this product, which is only for intravenous administration, with Cortrosyn, which can be administered by both the intramuscular and intravenous routes of administration. We believe there is a distinct possibility that the Sandoz product may be confused as a generic equivalent to the

Organon product because it will be marketed without a proprietary name. Health care practitioners are accustomed to administering Cortrosyn by both routes of administration and will think that they can do the same with this product.

After discussion with the DMEP medical officer, DMETS has learned that, currently, it is unknown how serious a local reaction would occur if this product were accidentally injected intramuscularly. If there is a potential for a medically serious adverse reaction after intramuscular injection, DMETS recommends that this product be reformulated so that it can be administered by both the intramuscular and intravenous routes of administration. If minimal reaction is expected post intramuscular administration then an educational campaign relating to the differences between this product and Cortrosyn should be implemented.

2. To further minimize the risk of inadvertent intramuscular administration as described above, a boxed warning should be added to the container label that states:

Note: For Intravenous Use Only
Not to be administered by the intramuscular route.

3. Because this product can only be given by intravenous administration, it is important to highlight this difference from Cortrosyn. Thus, we request that you revise the route of administration statement to read as described above or, at a minimum, bold the current statement and revise 'For IV Use' to read "For Intravenous Use Only", and increase the prominence of this statement by bolding, boxing, or some other means. The reason we want 'IV' spelled out is that FDA launched a campaign in June 2006, warning healthcare providers and consumers not to use error-prone abbreviations. Thus, we request that the OND Divisions not approve or use abbreviations in their labels and labeling as they can be misinterpreted (e.g., the abbreviation 'IV' which can be misinterpreted as the Roman Numeral 4 and contribute to error.
4. We note the Cortrosyn labels use similar colors with their trade dress (blue on white background). We strongly recommend Sandoz revise their color scheme so that their labels and labeling look entirely different than Organon's Cortrosyn. This visual similarity in conjunction with the fact that the Sandoz product will not have a proprietary name increases the risk of product interchangeability and selection errors.
5. The presentation of the sponsor's name and log is more prominent than the established name. Revise the presentation so that the proprietary and established names are the most prominent information on the primary display panel.
6. Include a net quantity statement on the principal display panel (e.g. 1 mL) and ensure that it is not in close proximity to the strength. We refer you to 21 CFR 201.51 for further guidance.

B. CONTAINER LABEL

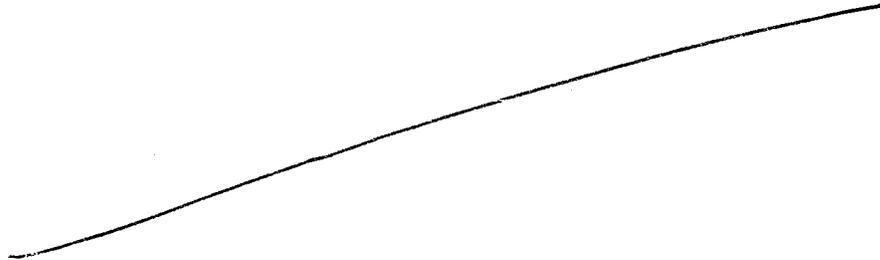
See GENERAL COMMENTS A3 through A7.

C. CARTON LABELING

1. See GENERAL COMMENTS A3 through A7.
2. Decrease the size of the 'FOR DIAGNOSTIC USE ONLY' statement.
3. Revise the '10 Single-Dose Vials' statement to say '10 X 1 mL single dose vials'.

D. INSERT LABELING

1.



b(4)

2. The DOSAGE AND ADMINISTRATION Section, second paragraph lists the steps for a 'rapid screening test'. However, these steps appear in reverse order, (e.g. control sample collected, injection of drug, then visual inspection of the drug prior to injection). Revise the directions to provide for a logical flow of activities for the administration of this drug. For example: (1) collect a 6-7 mL sample of blood in a heparinized tube, (2) visually inspect the drug for particulate matter....., (3) Inject 1 mL of the cosyntropin).
3. The DOSAGE AND ADMINISTRATION Section refers to adding Cosyntropin Injection to glucose solutions. Since there are multiple strengths of glucose containing intravenous fluids (e.g. 5% Dextrose, 10% Dextrose, etc.), DMETS recommends that compatible strengths be identified in the package insert. Additionally, this section also refers to 'saline solutions'. The word saline is defined by Dorland's Medical Dictionary¹ as 'salty; of the nature of a salt; containing a salt or salts'. Clearly identify which 'saline' solution and recommended volume is compatible with this product, (for example: 0.9 % Sodium Chloride for Injection, USP).
4. Add a statement to the DOSAGE AND ADMINISTRATION section that states that this product should not be given intramuscularly.

¹ www.dorlands.com

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/s/

Linda Wisniewski
8/11/2006 11:56:03 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
8/11/2006 04:01:02 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/11/2006 04:13:06 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (Division/Office): DD MAC

FROM: Jena Weber, PM
Division of Metabolism & Endocrinology Products

DATE: 4/17/06

NDA: 22-028

TYPE OF DOCUMENT: PPI, carton
& container labels

DATE OF DOCUMENT: 2/3/06

NAME OF DRUG: Cosyntropin
Injection 0.25 mg/mL

PRIORITY CONSIDERATION: NO

CLASSIFICATION OF DRUG:
Diagnostic agent to screen
for adrenocortical
insufficiency

DESIRED COMPLETION DATE:
September 1, 2006

NAME OF FIRM: Sandoz Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> LABELING |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|---|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input checked="" type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

Comments: Original NDA Submission. Please review and comment prn on all proposed LBL. Each section (PI, carton & container) is available via EDR. **User Fee Goal Date: 12/6/06.**

SIGNATURE OF REQUESTER: Jena Weber, PM
301-796-1306.

METHOD OF DELIVERY: DFS

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Kanika Vij
7/11/2006 03:19:29 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

*****PRE-DECISIONAL AGENCY INFORMATION*****

Date: July 11, 2006

To: Jena Weber, PM
Division of Metabolic and Endocrine Products

From: Kanika Vij, Pharm.D.
Division of Drug Marketing, Advertising, and Communications

Subject: Drug: Cosyntropin Injection 0.25mg/mL
NDA: 22-028

DDMAC has reviewed the proposed product labeling as well as carton and container labeling for cosyntropin injection 0.25 mg/mL and we have no comments on these at this time.

If you have any questions or concerns regarding my comments, please contact me.

**APPEARS THIS WAY
ON ORIGINAL**

Thank you. If you have any questions, please contact Kanika Vij at 301.796.0580 or Kanika.Vij@fda.hhs.gov

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/s/

Kanika Vij
7/11/2006 03:07:55 PM
DDMAC REVIEWER

| | | | | |
|---|--------------------------|---|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 | | FROM: DEMP Jena Weber, PM | | |
| DATE: 4/17/06 | IND NO. 69,720 | NDA NO. 22-028 | TYPE OF DOCUMENT Tradename Proposal | DATE OF DOCUMENT 2/3/06 |
| NAME OF DRUG: Cosyntropin Injection 0.25 mg/mL | | PRIORITY CONSIDERATION S | CLASSIFICATION OF DRUG: Diagnostic agent to screen for adrenocortical insufficiency | DESIRED COMPLETION DATE September 1, 2006 |
| NAME OF FIRM: Sandoz Inc. | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review | | | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | STATISTICAL APPLICATION BRANCH | | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): | | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILTY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | | <input type="checkbox"/> PRECLINICAL | | |
| COMMENTS/SPECIAL INSTRUCTIONS: Review and comment on proposed tradename. PDFA DATE: 12/6/06 ATTACHMENTS: Package Insert, Container and Carton Labels – available via EDR | | | | |
| NAME AND PHONE NUMBER OF REQUESTER Jena Weber, 301-796-1306 | | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND | | |
| SIGNATURE OF RECEIVER | | SIGNATURE OF DELIVERER | | |

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/s/

Jena Weber

4/17/2006 07:28:27 AM



DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: April 14, 2006

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Mary Parks, M.D.
Acting Director, Division of Metabolism and Endocrinology Products

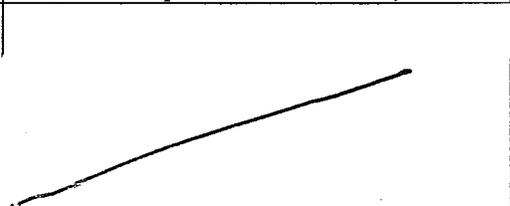
FROM: Jena Weber, Regulatory Project Manager, HFD-510

SUBJECT: Request for Biopharmaceutical Inspections
NDA 22-028
Cortrosyn (cosyntropin) for Injection

Study/Site Identification:

As discussed with you, the following study/site pivotal to approval has been identified for inspection:

Study entitled, "A Randomized, Open-Label, 2-Way Crossover, Bioequivalence, Pharmacodynamic Endpoint Study of Cosyntropin 0.25 mg/mL Injection and Cortrosyn (reference) Following a 0.25 mg IV Dose in Healthy Subjects."
Date of final report: December 12, 2005.

| Study # | Clinical Site (name, address, phone, fax, contact person, if available) | Analytical Site (name, address, phone, fax, contact person, if available) |
|---------|---|---|
| 50525 |  | Same |

b(4)

International Inspections:

We have requested an international inspection because:

There is a lack of domestic data (none) that solely supports approval;

Other (please explain):

Goal Date for Completion:

We request that the inspection be conducted and the Inspection Summary Results be provided by **September 1, 2006**. We intend to issue an action letter on this application by **December 6, 2006**.

Should you require any additional information, please contact Ms. Jena Weber at 301-796-1306.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Eric Colman
4/14/2006 09:42:43 AM
Eric Colman for Mary Parks

Weber, Jena M

From: Wei, Xiaoxiong
Sent: Thursday, April 06, 2006 4:01 PM
To: Weber, Jena M
Cc: Ahn, Hae Young
Subject: NDA22-028 DSI inspection information

Hi Jena,

Per filing meeting, I provide the following information for DSI inspection for NDA22-028 for Cosyntropin:

Study code: 50525

Title:

Randomized, Open-Label, 2-Way Crossover, Bioequivalence, Pharmacodynamic Endpoint Study of Cosyntropin 0.25 mg/mL Injection and Cortrosyn (Reference) Following a 0.25 mg Intravenous Dose In Healthy Subjects

Date of Final Report: 2005-12-12

Investigators: _____

Study Centre [Clinical, statistical, and analytical]:

b(4)

Please let me if you need additional information.

Thanks!

Jim

4/10/2006

REQUEST FOR CONSULTATION

TO (Division/Office): OPS, Attention: David Hussong, Ph.D.
FD-805

FROM: DEMP
Jena Weber, PM

DATE
2/24/06

IND NO.

NDA NO.
22-028

TYPE OF DOCUMENT: NDA

DATE OF DOCUMENT
2/3/06

NAME OF DRUG
Cosyntropin (α 1-24
corticotropin) for Injection

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG
Diagnostic agent

DESIRED COMPLETION DATE
9/06/06

NAME OF FIRM: Sandoz

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
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 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review and comment on microbiology controls proposed for the drug substance, drug product, etc, as applicable. NDA is an electronic submission, although paper volumes are available.
PDUFA DATE: 12/06/06

NAME AND PHONE NUMBER OF REQUESTER
 Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
 DFS ONLY MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

David Hussong
2/24/2006 03:02:11 PM

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

| | |
|--|---|
| 1. APPLICANT'S NAME AND ADDRESS SANDOZ CANADA INC. (formerly Sabex 2002) 145 Jules Leger Street Boucherville (QC) Canada J4B 7K8 | 4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER |
| 2. TELEPHONE NUMBER (Include Area Code) (450) 641-4903 (US Agent: 303 438-4237) | 5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA). |
| 3. PRODUCT NAME Cosyntropin Injection 0.25mg/mL | 6. USER FEE I.D. NUMBER |

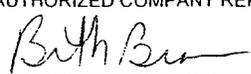
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

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

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

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

| | | |
|--|--|--|
| Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 | Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 | An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. |
|--|--|--|

| | | |
|---|--|---------------------|
| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  | TITLE Beth Brannan, Director Regulatory Affairs US Authorized Agent for Sandoz Canada Inc. | DATE FEB 03 2006 |
|---|--|---------------------|

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Wednesday September 22, 2004
TIME: 3:00 pm
LOCATION: 3rd floor Parklawn, Chesapeake Room
APPLICATION: P-IND 69,720 (Cosyntropin) Injection
TYPE OF MEETING: Pre-NDA
MEETING CHAIR: David Orloff, M.D., Division Director, Metabolic and Endocrine Drug Products (DMEDP), HFD-510
MEETING RECORDER: Jena Weber, Project Manager

Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510:

| | |
|---------------------------|--|
| David Orloff, M.D. | Division Director |
| Robert Perlstein, M.D. | Clinical Reviewer |
| Jeri El-Hage, Ph.D. | Team Leader – Pharmacology |
| Eric Duffy, Ph.D. | Division Director, Office of New Drug Chemistry II |
| Mamta Gautam-Basak, Ph.D. | Team Leader - Chemistry |
| Martin Haber, Ph.D. | Chemistry Reviewer |
| Jena Weber, BS | Project Manager |

Office of Clinical Pharmacology and Biopharmaceutics, HFD-870

| | |
|--------------------------|--------------------------------|
| Hae-Young Ahn, Ph.D. | Team Leader - Biopharmaceutics |
| Jaya Vaidyanathan, Ph.D. | Biopharmaceutics Reviewer |

Microbiology, HFD-805

| | |
|-------------|-----------------------|
| James McVey | Microbiology Reviewer |
|-------------|-----------------------|

Sabex Inc:

| | |
|------------------------------|------------------------------|
| Leonor Ferreira, MS, MBA | Director, Scientific Affairs |
| Suzanne Levesque, R.Ph., MBA | VP QA & Scientific Affairs |
| Alain Carrier, Ph.D | Director, R&D |
| Sonia Gallo, BSc | Manager, Medical Affairs |

Proposed Indication: Diagnostic screening agent used in patients presumed to have adrenocortical insufficiency.

Purpose of Meeting: Requirements for filing a 505(b)(2) NDA.

Questions for Discussion:

1. Is the product eligible for an application under section 505(b)(2)?

FDA Response: Possibly yes. However, the Agency has not established specific guidelines and qualifications for proteins and some biologic products on what products are eligible to be submitted as 505(b)(2)'s. We will work with the company to assure a swift and appropriate review process.

2. Can the requirements under the following section be waived for Sabex' formulation of Cosyntropin Injection?

- 21CFR 314.126 Adequate and well-controlled studies?
- 21CFR 320.21 Requirements for submission of in vivo bioavailability and bioequivalence data?

FDA Response: If the route of administration is IV, there is no prerequisite for pharmacokinetic data. The determination to waive well-controlled studies is predicated on structural identity of the protein product. Therefore, it is essential that Identity be established, as amino acid sequence may not be completely sufficient to waive such studies. An Impurity Profile should also be provided.

A pharmacodynamic (PD) study may be required to demonstrate that the test drug product contains the same active ingredient (i.e., no difference in tertiary structures), as the reference drug product (RDP). If IM administration is designated as the route of administration, a bioequivalence (BE) study between the test drug and RDP will be necessary since there is a difference in the formulations with respect to the buffer and presence of mannitol. If the test product contains mannitol, and it is demonstrated that pH and isotonicity of cosyntropin and the reference product is identical, the BE study could possibly be waived.

3. Can the requirements to supply information on clinical, pharmacology and toxicology supported by published literature suffice for a 505(b)(2) application?

FDA Response: This is dependent upon the qualification of the impurity profile. Novel impurities or an impurity profile significantly different from the reference product may necessitate bridging toxicology studies.

4. If the requirements for submission of in vivo bioavailability and bioequivalence data can not be waived, will performing the diagnostic test (control blood sample and one time point) as indicated in the innovator labeling on subjects with both the Sabex and RLD products suffice? The number of subjects will be determined following a pilot study.

FDA Response: A randomized, blinded, two-way crossover PD study should be conducted using plasma cortisol levels as the pharmacodynamic end point.

5. Will AB rating be granted to Sabex' product if the product meets the bioequivalence criteria?

FDA Response: The Orange Book staff, in consultation with the review Division will determine the appropriate rating for this product. The labeling will reflect language that is interchangeable with the registered product, and data from studies (if applicable) exclusive to the Sabex product.

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

/s/

Jena Weber
9/29/04 09:46:28 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| | | |
|---|--------------------------|--|
| NDA 22-028 | Efficacy Supplement Type | Supplement Number |
| Drug: Cosyntropin Injection 0.25 mg/mL | | Applicant: Sandoz |
| RPM: Jena Weber | | DMEP Phone: 301-796-1306 |
| <p>Application Type: () 505(b)(1) (<input checked="" type="checkbox"/>) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>(<input checked="" type="checkbox"/>) Confirmed and/or corrected</p> | | <p>Listed drug referred to in 505(b)(2) application (NDA), Drug name: NDA 16-750 CORTROSYN for Injection, Amphastar</p> |
| ❖ Application Classifications: | | |
| • Review priority | | (<input checked="" type="checkbox"/>) Standard () Priority |
| • Chem class (NDAs only) | | |
| • Other (e.g., orphan, OTC) | | |
| ❖ User Fee Goal Dates | | 2/21/08 |
| ❖ Special programs (indicate all that apply) | | <input checked="" type="checkbox"/> None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2 |
| ❖ User Fee Information | | |
| • User Fee | | Not paid |
| • User Fee waiver | | () Small business () Public health () Barrier-to-Innovation () Other (specify) |
| • User Fee exception | | () Orphan designation (<input checked="" type="checkbox"/>) No-fee 505(b)(2) () Other (specify) |
| ❖ Application Integrity Policy (AIP) | | |
| • Applicant is on the AIP | | () Yes (<input checked="" type="checkbox"/>) No |
| • This application is on the AIP | | () Yes (<input checked="" type="checkbox"/>) No |
| • Exception for review (Center Director's memo) | | NN |
| • OC clearance for approval | | For AE (11/20/06) 2/20/08 (505b2 staff) |

Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

| | |
|---|--|
| <p>❖ Exclusivity (approvals only)</p> | |
| <ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) | <p>NO</p> |
| <ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. | <p><input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No</p> |
| <p>❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</p> | <p>✓</p> |

| | |
|--|--|
| ❖ Actions | |
| • Proposed action | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA |
| • Previous actions (specify type and date for each action taken) | AE 12/6/06 |
| • Status of advertising (approvals only) | <input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | <input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | |
| • Most recent applicant-proposed labeling | 2/15/08 |
| • Original applicant-proposed labeling | 2/3/06 |
| • Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) | DMETS – 8/11 & 11/2/06, 12/20/06. DDMAC – 7/11/06 |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | NA |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | |
| • Applicant proposed | 12/4/06 |
| • Reviews | 12/20/06 (DMETS) |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | None |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | NN |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | <input checked="" type="checkbox"/> |
| ❖ Memoranda and Telecons | <input checked="" type="checkbox"/> |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | NA |
| • Pre-NDA meeting (indicate date) | 9/22/04 |
| • Pre-Approval Safety Conference (indicate date; approvals only) | NN |
| • Other | NN |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | NN |
| • 48-hour alert | NN |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | NN |

| Summary Approval Review | |
|--|--|
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i> | DD: 2/21/08 MO TL: 12/5/06 CMC TL: 1/30/08 |
| Clinical Information | |
| ❖ Clinical review(s) <i>(indicate date for each review)</i> | 11/27/06 |
| ❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i> | 12/04/06, 1/16/08 |
| ❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i> | NN |
| ❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i> | NN |
| ❖ Pediatric Page (separate page for each indication addressing status of all age groups) | 2/1/08 |
| ❖ Demographic Worksheet <i>(NME approvals only)</i> | NN |
| ❖ Statistical review(s) <i>(indicate date for each review)</i> | NN |
| ❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i> | 12/01/06 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i> | NN |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | NN |
| • Bioequivalence studies | 11/28/06 |
| CMC Information | |
| ❖ CMC review(s) <i>(indicate date for each review)</i> | 11/15/06, 1/24/08 |
| ❖ Environmental Assessment | |
| • Categorical Exclusion <i>(indicate review date)</i> | 11/15/06 |
| • Review & FONSI <i>(indicate date of review)</i> | NN |
| • Review & Environmental Impact Statement <i>(indicate date of each review)</i> | 11/15/06 |
| ❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i> | 12/04/06, 1/16/08 |
| ❖ Facilities inspection (provide EER report) | Date completed: <input checked="" type="checkbox"/> Acceptable 11/27/06 <input type="checkbox"/> Withhold recommendation |
| ❖ Methods validation | <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not requested |
| Nonclinical Pharm/Tox Information | |
| ❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i> | 10/03/06, 1/16/08 |
| ❖ Nonclinical inspection review summary | NN |
| ❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i> | NN |
| ❖ CAC/ECAC report | NN |