

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 1, 2007
TIME: 2:30 pm to 3:30 pm EST
LOCATION: FDA , White Oak
APPLICATION: IND 69,927
DRUG NAME: Dexlansoprazole (b) (4) Capsules
TYPE OF MEETING: Type B

MEETING CHAIR: Dr. Ruyi He

MEETING RECORDER: Chantal Phillips

FDA ATTENDEES:

Division of Gastroenterology Products

Joyce Korvick, M.D., M.P.H., Deputy Director
Ruyi He, M.D., Medical Team Leader
Marjorie Dannis, M.D., Medical Reviewer
Sushanta Chakder, Ph.D., Pharmacology Reviewer
Ke Zhang, Ph.D., Pharmacology Reviewer

Division of Biometrics III

Mike Welch, Ph.D, Statistical Team Leader

Office of Clinical Pharmacology and Biopharmaceutics

Sue-Chih Lee, Ph.D., Team Leader
Jane Bai, Ph.D., Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Nancy Joseph-Ridge, MD, Vice President, Research and Development, TAP
Dean Sundberg, Vice President, Regulatory Affairs, TAP
Donna Helms, BS, MBA, RAC, Director, Regulatory Affairs, TAP
Nancianne Knipfer, PhD, RAC, Principal Regulatory Adviser, TAP
Stuart Atkinson, MD, Senior Scientific Director, Head Therapeutic Areas, TAP
Robert Jackson, MD, Head of Clinical Development, Outcomes and External Research, TAP
Maria Claudia Perez, MD, Medical Director, GI Therapeutic Areas
Maria Paris, MD, PhD, Senior Director, Clinical Safety Pharmacovigilance, TAP
Nancy Siepman, PhD, Director, Statistics and Study Programming, TAP
Galen Witt, Assistant Director, Statistics, TAP
Steve Elrod, Vice President, Scientific Affairs, TAP
Darcy Mulford, PhD, Director, Drug Metabolism and Pharmacokinetics, TAP
Harriet Glassman, Senior Director, Project Management, Operations, and Scientific Communications, TAP
Takeshi Seita, Takeda Liaison, TAP

BACKGROUND:

Tap Pharmaceutical Products submitted a Pre-NDA meeting for Dexlansoprazole on June 18, 2007. Dexlansoprazole is currently under a Tradename review and the proposed indication is for healing of erosive esophagitis; maintenance healing of erosive esophagitis (b) (4) and treatment of (b) (4) heartburn. Tap Pharmaceutical Products plans to submit an NDA in late 2007.

MEETING OBJECTIVES:

The objective of the meeting is to discuss non-clinical and clinical information related to Dexlansoprazole.

DISCUSSION POINTS:

In response to questions in the August 9, 2007, background package, the following responses were given. The format provides the firm's questions in italics followed by FDA responses in bold lettering. Questions, responses, and additional comments are indicated with headings.

CLINICAL QUESTIONS

Question 1.

As planned in the protocols, Studies T-EE04-084 and T-EE04-085 were designed to demonstrate noninferiority of dexlansoprazole MR 60 mg and 90 mg to lansoprazole 30 mg for the healing of EE, and, if noninferiority was established for either or both doses in these studies, superiority to lansoprazole 30 mg would also be assessed. Results from both of these studies demonstrate noninferiority of dexlansoprazole MR 60 mg and 90 mg to lansoprazole 30 mg for the healing of EE in the primary analysis (life-table method). In addition to achieving noninferiority to lansoprazole 30 mg for the primary efficacy endpoint for both dexlansoprazole MR 60 mg and 90 mg in 2 studies,

Does the Agency agree that these studies are adequate to support the approval of dexlansoprazole MR for the EE healing indication?

FDA Response:

The adequacy of the studies to support approval will be determined during the review process. Non-inferiority studies, in particular, require a substantial level of justification to support the chosen margin, assay sensitivity and constancy of control assumptions. (Refer

to ICH E10). Regarding your multiple objectives, you will need to clearly establish prospectively defined procedures for experiment-wise Type I error control

Additional Comment:

The sponsor concurred with these requirements and indicated they will be documented within their submission.

Question 2.

Studies T-EE04-084 and T-EE04-085 are identical in design and have similar patient populations and baseline characteristics. In order to provide additional statistical power to evaluate subjects with moderate to severe grades of EE (Los Angeles [LA] Classification Grades C and D [23% and 6% of overall enrolled subjects, respectively]), TAP plans to present an analysis of combined data from both studies to demonstrate efficacy of dexlansoprazole MR in Grades C and D combined. Does the Agency agree that the combined analysis from the 2 EE healing studies demonstrates the added clinical benefit of dexlansoprazole MR 90 mg over lansoprazole 30 mg in Grades C and D?

FDA Response:

We do not agree. The combining or pooling of studies to show a clinically and statistically significant effect within a subgroup would generally be considered an exploratory analysis. The statistical significance and clinical benefit of *dexlansoprazole MR 90 mg over lansoprazole 30 mg* should be demonstrated within the individual studies as prospectively planned.

Additional Comment:

We discussed the concept that the individual studies will be the primary data and the combined analysis will be used as supportive data. The significance of the combined analysis will be a review issue.

Question 3.

Does the Agency agree with the proposed dosing recommendations for EE healing?

FDA Response:

The adequacy of the studies to support approval will be determined during the review process.

Question 4.

TAP conducted 2 large, robust Phase 3, controlled studies in subjects with healed EE (T-EE04-086 and T-EE05-135). As discussed with the Agency in the 01 March 2006 teleconference, both studies included the 60-mg dose, and only one of these studies (T-EE05-135) included the 30-mg dose. Does the Agency agree that the single study (T-EE05-135), a large, adequate, and well-controlled study that demonstrates clinically and statistically significant superiority of dexlansoprazole MR 30 mg and 60 mg over placebo ($p < 0.00001$), is acceptable for the approval of dexlansoprazole MR for the maintenance of healed EE indication?

FDA Response:

A single superiority study would need to demonstrate high statistical significance with demonstrable clinical efficacy. A single study would need to show consistent results across subgroups, centers, secondary endpoints, and other factors. Adequacy of the studies to support approval would be determined during the review process.

Question 5.

Based on subgroup analysis for Grades C and D, dexlansoprazole MR 60 mg demonstrated a higher percentage of subjects with maintenance of healed EE than dexlansoprazole MR 30 mg in Study T-EE05-135. This was also observed using combined data from Studies T-EE05-135 and T-EE04-086. Does the Agency agree that these data demonstrate the added clinical benefit of dexlansoprazole MR 60 mg in Grades C and D combined?

FDA Response:

Unplanned or retrospective subgroup analyses are considered exploratory and would not support labeling claims. During the review process, subgroup differences may be found

that would appear to be of clinical significance; however, such results would generally need confirmation in a new, adequately controlled study. Also see response to question 2.

Question 6.

Does the Agency agree with the proposed dosing recommendations for maintenance of healed EE?

FDA Response:

The adequacy of the studies to support approval will be determined during the review process.

Question 7.

As discussed with the Agency in the 01 March 2006 teleconference, the primary analyses for studies to support the EE healing and maintenance of healed EE indications utilized life-table methods and the log-rank test was used for comparisons between treatment groups. For assessing these indications, does the Agency have any preference regarding choice of discrete time units (day-based or interval-based)?

FDA Response:

Life table methods may be informative; however, we recommend the primary analyses be based on proportions of subjects who are healed by a specific time point. Adequacy of your study design and analyses to support your indications will be determined during the review process.

Additional Comment:

We discussed the primary endpoint analysis. It was agreed that the sponsor will change their primary analysis to compare the proportions of patients responding at a specified time point, e.g., eight weeks,(crude rate analysis), and use the time to event, life- table method, as a supportive analysis.

Sponsor will submit an amendment in their submission to this effect.

Question 8.

In addition, does the Agency find the assumptions used to implement the life-table method as summarized in Appendix B acceptable, including the methods of censoring and the choice of discrete time units for estimating rates?

FDA Response:

Please refer to the response for question 7. Agency review of your statistical analysis plan is best accomplished prior to starting your phase 3 studies. As this is a preNDA meeting, we assume that at this time, your analysis plan has been prospectively defined and finalized. The adequacy of your analyses will be addressed during review of your submission.

Question 9.

Does the Agency agree that the single study (T-GD05-137), a large, adequate, and well-controlled study that demonstrated clinically and statistically significant superiority of dexlansoprazole MR 30 mg over placebo ($p < 0.00001$), is acceptable for approval of dexlansoprazole MR for the symptomatic GERD indication?

FDA Response:

A single study will need to demonstrate high statistical significance with consistent levels of efficacy across subgroups, centers, secondary endpoints, and other factors. This will be determined during the review process.

Question 10.

Does the Agency agree with the proposed dosing recommendations for symptomatic GERD?

FDA Response:

The adequacy of the studies to support approval will be determined during the review process.

Question 11.

Based on the pharmacodynamic and pharmacokinetic data from Study T-P106-146 summarized in Section 9.2.2, does the Agency agree that dexlansoprazole MR can be taken without regard to the timing of food?

FDA Response:

This is a review issue and will be determined during the review process.

Question 12.

- a) *The safety profile of dexlansoprazole MR is similar to lansoprazole and appears to be consistent with other proton pump inhibitors (PPIs). Does the Agency have any questions or concerns regarding the safety profile of dexlansoprazole MR based on the data summarized in the briefing document?*

FDA Response:

The adequacy of the studies to support approval will be determined during the review process.

- b) *Does the Agency agree that the long-term patient exposure data to be included in the original NDA and the 4-Month Safety Update (described in Table 9.4.1.a)) are adequate to support the NDA filing?*

FDA Response:

It is acceptable.

Question 13.

Does the Agency agree with the proposed strategy for the Integrated Summaries of Efficacy (ISE) and Summaries of Clinical Efficacy for each indication, as described in Section 12.1.1? Specifically:

- a) *TAP's proposal to split each of the ISEs for the healing of EE and maintenance of healed EE indications, as described in the June 2007 draft Guidance for Industry, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document." As described in Sections III.C and V.D of the draft guidance, TAP plans to place the text portion of each ISE in Module 2.7.4 (Summary of Clinical Efficacy) and the tables, appendices, and datasets in Module 5.3.5.3. Statistical tables referenced in the text (Module 2.7.4) will be electronically hyperlinked to the tables located in Module 5.*

FDA Response:

This appears to be acceptable; however, confirmatory evidence of efficacy should be based on the individual studies; data from the ISE are mainly used for supportive and/or exploratory purposes and do not constitute substantial evidence for labeling purposes.

- b) *TAP's proposal to have only a Summary of Clinical Efficacy and no ISE for the symptomatic GERD indication, as integration of the 2 symptomatic GERD studies is not warranted.*

FDA Response:

No.

Question 14.

Does the Agency have any questions or comments about the proposed study groupings or the data presentation for the Integrated Summary of Safety (ISS) as described in Section 12.1.2?

FDA Response:

No.

Question 15.

Does the Agency have any comments on the validation data for the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) and Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index (PAGI-QOL) questionnaires previously

submitted to IND 69,927 on 13 April 2006 (Serial No. 0039) and 10 August 2006 (Serial No. 0058)?

FDA Response:

Pending SEALD response. (Not addressed during meeting).

LABELING

Question 16.

For the NDA, the full prescribing information will be provided in portable document file (PDF) and Microsoft Word formats. Structured product labeling (SPL) will not be submitted with the NDA, but will be submitted after approval once the full prescribing information is agreed upon. Is this acceptable?

FDA Response:

No, we expect PLR and SPL format to be submitted with the original NDA submission. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf>], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Question 17.

For the NDA, labels for the primary packaging will be provided in Microsoft Word and PDF format as text, and color mock-ups will be submitted during the review. Is this acceptable?

FDA Response:

No, please submit with the original application.

OVERALL QUESTIONS

Question 18.

Has the Agency identified any issues that could affect the filing of the NDA under 21 CFR 314.101?

FDA Response:

This will be determined at the time of filing.

Question 19.

Has the Agency identified any review issues?

FDA Response:

This will be determined during the review process.

Regulatory

Question 20.

The NDA will contain financial disclosure for the following six Phase 3 studies, which meet the definition of a “covered study” per 21 CFR 54:

- *EE healing (T-EE04-084, T-EE04-085)*
- *Maintenance of healed EE (T-EE04-086, T-EE05-135)*
- *Symptomatic GERD (T-GD05-137, T-GD04-082)*

Financial disclosure will not be included for any Phase 1 study or for the Phase 3 Study T-GI04-088 (an uncontrolled, open-label, long-term extension study), as these studies are not considered “covered” studies per the regulations. Is this acceptable?

FDA Response:

No, the financial disclosure should be provided for all Phase 3 studies.

Question 21.

- a) *For the NDA, electrocardiogram (ECG) findings will be included in the data listings of each clinical study report. ECG tracings will be available upon request. Is this acceptable?*

FDA Response:

Yes, this is acceptable.

- b) *TAP plans to submit Council for International Organization of Medical Sciences (CIOMS) reports in place of text narratives for deaths and other serious adverse events (SAEs). Narratives for premature discontinuations due to adverse events will also be submitted. Is this acceptable?*

FDA Response:

No, you should provide text narrative for all patient deaths and serious adverse events as well as all premature discontinuations.

Additional Comment:

The CIOMS format is acceptable in place of text narratives for patient deaths and serious adverse events as long as all of the relevant information is included.

The patient profile format should be provided for all premature discontinuations.

- c) *The dexlansoprazole MR NDA will cross-reference lansoprazole clinical and nonclinical study reports previously submitted under IND 30,159 and NDA 20-406 for Prevacid (lansoprazole) Delayed-Release Capsules. TAP does not plan to resubmit these reports, but will include cross-references to their locations in the respective locations. Is this acceptable?*

FDA Response:

Yes.

Question 22.

Does the Agency have any questions or comments regarding the test submission with datasets in Clinical Data Interchange Standards Consortium (CDISC) format as submitted on 13 July 2007?

FDA Response:

CDISC format is acceptable.

NONCLINICAL QUESTIONS

Question 23.

The Agency and TAP discussed at the Type C meeting (teleconference) held on 06 October 2004 that based on FDA's Policy Statement for the Development of New Stereoisomeric Drugs, the following nonclinical studies would support the bridging strategy for dexlansoprazole, the R-enantiomer of lansoprazole:

- *In vitro Purkinje fiber study*
- *3-month repeat-dose toxicity study in rats*
- *3-month repeat-dose toxicity study in dogs*
- *Reproductive toxicity segment II study in rabbits*

In each in vivo study, lansoprazole was used as a comparator.

Additional nonclinical studies were performed including in vitro and in vivo pharmacodynamic and pharmacokinetic/drug metabolism studies, a 4-week, repeat-dose toxicity study in rats, and an Ames test with follow-up studies (Table 10.1.a). No additional studies are planned. Does the Agency agree that the above studies support the bridging strategy for filing an NDA for dexlansoprazole MR?

FDA Response:

No, please see our response to Question 24 below.

Question 24.

Has the Agency identified any issues based on the nonclinical study summaries provided in Section 10?

FDA Response:

Yes. Based on the results of the recent Ames tests, please conduct additional genotoxicity studies including an in vitro mouse lymphoma cell (b) assay or an in vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells, and an in vivo mouse micronucleus test.

Additional Comments:

Sponsor agrees to conduct the studies and plans to submit the draft report with the NDA submission.

We agree that sponsor can submit draft full reports with the initial NDA submission.

Office of Surveillance and Epidemiology (OSE)

Additional Comments:

- **If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and post marketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP). If you plan to submit a RiskMAP with the original submission, please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.**
- **For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:**

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

**Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>**

**Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>**

- **If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.**

DECISIONS (AGREEMENTS) REACHED:

See specific questions.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None.

ACTION ITEMS:

None.

ATTACHMENTS/HANDOUTS:

None.

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/s/

Ruyi He
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MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 10, 2008

TIME: 1:00 pm -3:00 pm

LOCATION: White Oak Central Shared Use (CSU) Building Room 2046

APPLICATION: NDA 22-287

DRUG NAME: Dexlansoprazole

TYPE OF MEETING: Regulatory Briefing

MEETING CHAIR: Sandra Kweder, MD

MEETING RECORDER: Chantal Phillips, LCDR, M.S.H.S., Regulatory Health Project Manager, DGP

PRESENTATION: Ruyi He, MD, Cross Discipline Team Leader
Tamara Johnson, MD, Medical Officer
Diane Wysowski, PhD., Epidemiologist
Jane Bai, PhD., Reviewer
Ke Zhang, PhD., Reviewer

FDA ATTENDEES: (Title and Office/Division)

See attached Sign In Sheet

EXTERNAL CONSTITUENT ATTENDEES:

None

BACKGROUND:

Dexlansoprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by inhibition of the (H⁺,K⁺)-ATPase enzyme system. Dexlansoprazole is the R-enantiomer of lansoprazole (PREVACID), a PPI which was approved in the US in 1995. Lansoprazole has a chiral center and equal proportions of 2 enantiomers: R- and S-lansoprazole. After oral administration of lansoprazole, Dexlansoprazole is the predominant circulating enantiomer, representing approximately 85% of the area under the plasma concentration-time curve (AUC). Dexlansoprazole has never been approved or marketed in any country.

TAP Pharmaceuticals, Inc. has developed Dexlansoprazole and seeks to demonstrate its use in treating the clinical conditions of gastroesophageal reflux disease (GERD) and erosive esophagitis (EE). Both of these conditions result from the frequent reflux of acidic stomach contents up into the esophagus. EE, however, distinguishes itself by the formation of painful erosions and ulcerations in the esophageal mucosa, and is diagnosed by endoscopy. In the US, reflux affects approximately 20% of adults weekly and 10% of adults daily, with 50% of those

affected developing mucosal damage.¹ EE leads to more severe complications, such as dysphagia, strictures, esophageal metaplasia (Barrett's esophagus), and adenocarcinoma. Where GERD may be treated with antacids, H₂-receptor antagonists, and short-term PPI use, treatment of EE requires more intense and long-term treatment with PPI's.

The proposed indications for Dexlansoprazole are: healing (b) (4) of all grades of erosive esophagitis (EE), maintaining healing of EE, and treating (b) (4) heartburn (b) (4)

MEETING OBJECTIVES:

To discuss safety issues (cardiovascular events and injury/fracture events) related to NDA 22-287 and decide whether these concerns warrant additional studies from the sponsor either prior to approval or post approval.

The attached slides were presented to the panel and discussed for clarification. Afterwards, the following questions were presented to the Panel.

Question 1:

Are you concerned by the excess AEs observed in the dexlansoprazole treatment groups compared to the lansoprazole or placebo group in the phase 3 studies? Do any of the categories of observed AEs constitute a safety signal?

- a. Cardiovascular events
- b. Fractures/injury-related events

Panel Response:

1. The Panel was not concerned by the excess AEs observed in the dexlansoprazole treatment groups compared to the lansoprazole or placebo group in the phase 3 studies. The Panel did not believe that the categories of observed AEs constituted a safety signal.

Question 2:

What is your recommendation for regulatory action?

- a. Complete Response with additional study to evaluate a specific safety signal
- b. Approval without an additional study
- c. Approval with PMR for additional study to evaluate a specific safety signal

Panel Response:

2. The Panel recommended approval without an additional study.

¹ Gastroesophageal Reflux Disease. Chapter 14. Gastrointestinal Disorders - *Kenneth R. McQuaid, MD*. CURRENT MEDICAL DIAGNOSIS & TREATMENT - 47th Ed. (2008). Lange Medical Books/McGraw-Hill, Medical Publishing Division: New York. <http://online.statref.com/document.aspx?fxid=27&doid=194>

Question 3:

What types of study do you recommend, if additional study is needed?

Panel Response:

3. The Panel discussed the possibility of a platelet aggregation study, but did not suggest a requirement of any additional studies.

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/s/

Anna Maria Simon
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DSI CONSULT: Request for Clinical Inspections

Date: March 5, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47
Name of DSI Primary Reviewer (if known)

Through: Consulting Review Division: Division of Gastroenterology Products/HFD-180
Keith St. Amand, M.D., Primary Medical Reviewer
Tamara Johnson, M.D., Medical Reviewer
Ruyi He, M.D., Medical Team Leader
Joyce Korvick, M.D., Deputy Director

From: Chantal Phillips, M.S.H.S., Regulatory Health Project Manager/Division of Gastroenterology Products/HFD-180

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-287
Sponsor: TAP Pharmaceutical Products
Nancianne Knipfer, Principal Regulatory Adviser
nancianne.knipfer@TAP.com
847-582-2193 phone
847-582-2880 fax

Drug: (dexlansoprazole) Delayed Release Capsules
NME: No
Standard or Priority: Standard
Study Population: Adults
Pediatric exclusivity: No

PDUFA Action Goal Date: October 31, 2008
Inspection Summary Goal Date: August 31, 2008

II. Background Information

IND 69,927 was submitted June 2, 2004. An End of Phase 2 meeting was held on May 12, 2005, and a Pre NDA meeting on October 1, 2007. This NDA also references IND 30,159.

About this application:

- New application or supplement? New application. Selected as a GRMP pilot application.
- Proposed indication:
 1. Healing (b) (4) relief of all grades of erosive esophagitis (EE).
 2. Maintaining healing of EE (b) (4)
 3. Treating (b) (4) heartburn (b) (4) associated with GERD.
- Brief information:

Lansoprazole, a PPI was approved May 10, 1995 for a variety of acid-related gastrointestinal disorders. Dexlansoprazole, an enantiomer of lansoprazole was developed to address unmet needs in GERD patients.

To further enhance the clinical benefit of dexlansoprazole, especially in treating patients with unmet medical needs, TAP Pharmaceutical Products Inc. (TAP) has developed an oral dual delayed release formulation of dexlansoprazole, referred to as dexlansoprazole MR. This formulation consists of 2 types of enteric-coated granules contained within a single capsule.

III. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
(b) (4)	T-EE04-084	161	Healing of EE
Site#18345 (b) (4)	T-GD04-082	38	Treatment of Symptomatic GERD

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
(b) (4)	T-GD05-137	33 27	Treatment of Symptomatic GERD

IV. Site Selection/Rationale

The sites above were selected on the basis of number of patients enrolled. These were the largest centers for each indication and provided the best cross-section of the patient population being studied.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

None requested

V. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Chantal Phillips at 301-796-2259.

Concurrence: (as needed)

Ruyi He, M.D., Medical Team Leader
 Keith St. Amand, M.D., Medical Reviewer
 Tamara Johnson, M.D., Medical Reviewer

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/s/

Chantal N. Phillips
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MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 20, 2008

TO: Chantal Phillips, M.S., Regulatory Project Manager
Keith St. Amand, M.D., Medical Officer
Division of Gastroenterology Products/HFD-180

FROM: Khairy Malek, M.D., Ph.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-287

APPLICANT: TAP Pharmaceutical Products

DRUG: Dexlansoprazole Delayed Release Capsules

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: 1. Healing (b) (4) of all grades of erosive esophagitis (EE).
2. Maintaining healing of EE (b) (4)
3. Treating (b) (4) heartburn (b) (4)
associated with GERD

CONSULTATION REQUEST DATE: March 5, 2008

DIVISION INSPECTION SUMMARY GOAL DATE: August 31, 2008
PDUFA DATE: October 31, 2008

1. BACKGROUND:

TAK-390MR is a proton pump inhibitor (PPI) and consists of the molecule of TAK-39 (enantiomer of lansoprazole) formulated as a modified release formulation, designed to produce an extended duration of action and to result in acid control over an entire 24 hour period and acceleration of healing of erosive esophagitis (EE).

The following protocols were inspected:

A. Protocol T-EE04-084: “A Phase 3 Study to Evaluate the Efficacy And Safety of TAK-390MR (60 mg QD and 90 mg QD) and an Active Comparator, Lansoprazole (30 mg QD) on Healing of Erosive Esophagitis (EE)”

The primary objectives of the study were to assess the efficacy of TAK-390MR, 60 and 90 mg daily compared to lansoprazole delayed release capsules 30 mg daily in healing EE over 8 weeks in subjects with endoscopically proven EE and to assess its safety.

B. Protocol T-GD04-083: “A Phase 3 Study to Evaluate the Efficacy and Safety of TAK-390MR (60 mg QD and 90 mg QD) Compared to Placebo on Symptom Relief in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease (GERD)”

The primary objectives of this protocol were to assess the efficacy of TAK-390MR, 60 and 90 mg daily compared to placebo in relief of daytime and nighttime heartburn over 4 weeks as assessed by daily electronic diaries, and to assess the safety of the study drug compared to placebo in subjects with symptomatic GERD.

C. Protocol T-GD05-137: “A Phase 3 Study to Evaluate the Efficacy and Safety of TAK-390MR (30 mg QD and 60 mg QD) Compared to Placebo on Symptom Relief in Subjects with Symptomatic Non-Erosive gastroesophageal Reflux Disease (GERD)”

The primary objectives of this study were to assess the efficacy of TAK-390MR 30 and 60 mg daily compared to placebo in relief of daytime and nighttime heartburn over 4 weeks as assessed by daily electronic diary and to assess the safety of 30 and 60 mg daily of the active drug compared to placebo.

II. RESULTS (by Site):

Name of CI Location	Protocol # and # of Subjects:	Inspection Dates	Final Classification
(b) (4)	T-EE04-084 – 161 subjects	April 24 – May 2, 2008	VAI
	1.T-GD04-083 – 38 subjects 2.T-GD05-137 – 33 subjects	June 13 – 19, 2008	VAI
	T-GD05-137 – 27 subjects	June 26-July 02/08	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. (b) (4)

- a. What was inspected: The field investigator reviewed the records of 40 subjects out of 151 subjects who completed the study.
- b. General observations/commentary: The inspection revealed three violations.
 - i) Inaccurate records: For subject # 007, the Medical History case report form (CRF) for the screening visit assessment date of 12/06/05 contains an entry regarding a sore throat that reportedly occurred from 12/13/05 to 12/16/05. This entry was crossed out on 12/6/05. In addition, the "Other Concomitant Medications" CRF, which is dated 12/6/05 and notes that all prescription and OTC medications taken within the last 30 days prior to the screen visit are to be recorded, contains among other entries an entry noting that amoxicillin was taken between 12/13/05 and 12/16/05 for sore throat. The remaining entries on this CRF are also for drugs taken subsequent to the visit date of 12/6/05. Also, for subject # 008, the Medical History CRF for the screening visit assessment date of 12/7/05 contains an entry regarding a hiatal hernia diagnosed on 12/15/05.
 - ii) Protocol violation: The protocol specified that subjects who are positive for H. pylori may be treated outside of the study and will be allowed to screen again after a minimum of 14 days post completion of eradication therapy. For subject # 64 who was positive for H. pylori at the randomization visit, the protocol was not followed in that an exemption code was sought to allow the subject to be randomized.
 - iii) Inaccurate records of the disposition of the drug: The drug accountability records of 5 subjects (# 144, 171, 204, 206 and 212) indicate that the site was unable to verify if Gelusil was returned.
- c. Assessment of data integrity: The above violations would not affect the validity of the data. The data from this site can be used in support of the NDA.

2. (b) (4)

- a. What was inspected: The field investigator reviewed the record of 12 subjects out of 37 who completed protocol T-GD04-83 and 15 subjects out of 31 subjects who completed protocol T-GD05-137.
- b. General observations/commentary: The inspection revealed two protocol violations: The electronic diaries were not reviewed or marked as reviewed by the clinical investigator, and the endoscopic pictures for two subjects (#001 and 004) were not included with the reports in their source documents as the protocol required.
- c. Assessment of data integrity: These protocol violations would not affect the validity of the data, and the data from this site can be used in support of the NDA.

3. (b) (4)

- a. What was inspected: The field investigator reviewed the records of all the subjects (24) who completed the study.
- b. General observations/commentary: The inspection revealed two violations:
 - i) Protocol violation: The endoscopy and the physical examination for subject # 138 were done by a physician who was not listed on the Form 1572.
 - ii) Inaccurate records: There were discrepancies between the source documents and the eCRFs in the number of rescue medication returned for 3 subjects (# 122, 136 and 156).
- c. Assessment of data integrity: These violations would not affect the validity of the data. The data from this site can be used in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from the three sites inspected are valid and can be used in support of the NDA

{See appended electronic signature page}

Khairy Malek, M.D., Ph.D.
Medical Officer
Good Clinical Practice Branch I
Division of Scientific Investigations

Dexlansoprazole Clinical Inspection Summary

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/

Khairy Malek
8/25/2008 01:39:01 PM
MEDICAL OFFICER

Constance Lewin
8/25/2008 02:07:49 PM
MEDICAL OFFICER

NDA SUPPLEMENT ACTION PACKAGE CHECKLIST SIGN-OFF SHEET

Application Information

NDA 22-287			
Drug: Kapidex (dexlansoprazole) Delayed – Release Capsules		Applicant: Takeda Global Research and Development Center	
RPM: Anna Simon		HFD-180	Phone # 301-796-3509
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:			
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)		2	
• Other (e.g., orphan, OTC)			
❖ User Fee Goal Dates		October 31, 2008 (Original date) January 31, 2009 (Major Amendment)	

Reviewers Sign Off List

Ruyi He, M.D., Medical Team Leader *Ruyi He* 1/30/09

Brian Strongin, R.Ph., M.B.A., Chief Regulatory Project Manager *B Strongin* 2/2/09

Donna Griebel, M.D., Division Director *Donna Griebel* 1/30/09

Appears This Way On Original

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22,287 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Kapidex Established/Proper Name: Dexlansoprazole Dosage Form: Delayed Release Capsules		Applicant: Takeda Global Research and Development Center Agent for Applicant (if applicable):
RPM: Anna M. Simon		Division: Division of Gastroenterology Products
<p>NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date October 31, 2008 (Original date) Action Goal Date (if different) January 31, 2009 (Major Amendment)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 2 <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	12-3-08
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, 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 the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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," 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 section below (Summary Reviews).

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	<input checked="" type="checkbox"/> Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 1-30-09
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	1-28-09
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12-28-07
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	1-28-09
<ul style="list-style-type: none"> Original applicant-proposed labeling 	12-28-07
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	1-13-09; 1-23-09
❖ Labeling reviews (indicate dates of reviews and meetings)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 8-22-08, 12-12-08 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 1-15-09 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD 1-22-09; Maternal Health 1-16-09
❖ Proprietary Name	
<ul style="list-style-type: none"> Review(s) (indicate date(s)) Acceptability/non-acceptability letter(s) (indicate date(s)) 	8-4-08, 9-12-08, 12-12-08 Acceptable 12-12-08
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	2-15-08
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (indicate date) If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing communications (if located elsewhere in package, state where located) 	12-19-09
<ul style="list-style-type: none"> Incoming submissions/communications 	1-12-09
❖ Postmarketing Commitment (PMC) Studies	<input checked="" type="checkbox"/> None

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

<ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	
<ul style="list-style-type: none"> Incoming submission documenting commitment 	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	1-4-08, 3-13-08, 5-1-08, 5-20-08, 6-6-08, 6-27-08, 8-13-08, 8-22-08, 8-28-08, 10-15-08, 11-5-08, 12-19-08, 12-22-08
❖ Internal memoranda, telecons, etc.	3-20-08, 10-29-08, 11-12-08, 1-13-09, 1-13-09, 1-28-09
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date; approvals only</i>) 	<input type="checkbox"/> Not applicable 12-3-08
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date</i>) 	<input type="checkbox"/> No mtg 10-10-08
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg 10-1-07
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-30-09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-30-09
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	See CDTL Review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	9-25-08; 1-27-09
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	8-27-08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Location: Clinical Review by Dr. St. Amand, pg 12, 9-25-08
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) REMS Memo (<i>indicate date</i>) REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	<input type="checkbox"/> None OSE 8-27-08 (see Safety Update Review Tab); Cardiovascular and Renal Products 8-19-08; Pediatrics 9-5-08
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 8-25-08, 9-8-08, 11-19-08
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-8-08, 1-6-09, 1-6-09
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12-3-08, 12-16-08
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12-2-08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2-14-08, 12-22-08, 1-26-09
• BLAs only: Facility information review(s) (<i>indicate dates</i>)	<input type="checkbox"/> None

<ul style="list-style-type: none"> ❖ Microbiology Reviews <ul style="list-style-type: none"> • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i> • BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Environmental Assessment (check one) (original and supplemental applications) 	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	12-22-08
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> ❖ Facilities Review/Inspection 	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: 1-16-09 <input checked="" type="checkbox"/> Acceptable (CMC review 1-26-09) <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

Anna Maria Simon
2/2/2009 03:34:30 PM

Memorandum****PRE-DECISIONAL AGENCY MEMO****

Date: January 15, 2009

To: Anna Simon, Regulatory Project Manager
Chantal Phillips, Regulatory Health Project Manager
Division of Gastroenterology Products

From: Shefali Doshi, Consumer Safety Officer
Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Robert Dean, Group Leader, DDMAC
Sangeeta Vaswani, Acting Group Leader, DDMAC

Subject: NDA 22-287
DDMAC labeling comments for Kapidex (dexlansoprazole) Delayed Release Capsules

DDMAC has reviewed the proposed product labeling (PI) and proposed patient labeling (PPI), for Kapidex (dexlansoprazole) Delayed Release Capsules (Kapidex) submitted for consult on January 12, 2009.

The following comments are provided using the "Annotated Label V10 08Jan" version of the proposed PI and PPI. DDMAC's comments are provided directly in the attached document (please see below).

We also acknowledge the comments made by SEALD on January 13, 2009, and make reference to those comments in the pertinent sections.

Please also apply the specific recommendations made for the proposed PI to the Highlights section, where applicable.

Thank you for the opportunity to comment on this proposed label. If you have any questions on the PI, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions on the PPI, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

Appears This Way On Original

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

/s/

Kathleen Klemm
1/15/2009 03:08:28 PM
DDMAC PROFESSIONAL REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-287 Supplement # Efficacy Supplement Type SE-

Proprietary Name: (b) [REDACTED]
Established Name: (dexlansoprazole) Delayed Release Capsules
Strengths: 30mg, 60mg, (b) [REDACTED]

Applicant: TAP Pharmaceutical Products
Agent for Applicant (if applicable):

Date of Application: December 28, 2007
Date of Receipt: December 31, 2007
Date clock started after UN:
Date of Filing Meeting: February 14, 2008
Filing Date: February 29, 2008

Action Goal Date (optional): August 31, 2008 User Fee Goal Date: October 31, 2008

Indication(s) requested: Healing (b) (4) [REDACTED] of all grades of EE
Maintaining healing of EE (b) (4) [REDACTED]
Treating (b) (4) [REDACTED] heartburn (b) (4) [REDACTED] associated with GERD

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
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 or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 2
Other (orphan, OTC, etc.)

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

User Fee Status: 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 by contacting the User Fee staff in the Office of Regulatory Policy. 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 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 any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? 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)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fn1.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?
Module 2-5

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification 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 . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 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 NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
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.
- List referenced IND numbers: 69,927 and 30,159
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) May 12, 2005 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) October 1, 2007 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 14, 2007

NDA #: 22-287

DRUG NAMES: (dexlansoprazole) Delayed Release Capsules

APPLICANT: TAP Pharmaceutical Products

BACKGROUND: Dexlansoprazole is the R-enantiomer of lansoprazole. This is a new NDA and is being reviewed under the GRMP pilot program.

ATTENDEES: T. Johnson, J. Bai, M. Welch, S. Chakder, K. Zhang, Mehta, T., S. Grosser, M. Kowblansky, R. He, C. Phillips

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

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Keith St. Amand
Secondary Medical:	Tamara Johnson
Statistical:	Stella Grosser
Pharmacology:	Ke Zhang
Statistical Pharmacology:	
Chemistry:	Tarun Mehta
Environmental Assessment (if needed):	
Biopharmaceutical:	Jane Bai
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Chantal Phillips
Other Consults:	QTIRT

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

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
 If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO