

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-287

OTHER REVIEW(S)



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Maternal Health Team Review

Date: January 13, 2009 **Date Consulted:** January 9, 2009

From: Jeanine Best, MSN, RN, PNP
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Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Gastroenterology Products (DGP)

Drug: Kapidex (dexlansoprazole), NDA 22-287

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Kapidex labeling.

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of labeling.

BACKGROUND

The Maternal Health Team (MHT) and the Safety Endpoints and Labeling Development (SEALD) Team have been working together to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

On January 9, 2009, SEALD requested MHT’s review of the Pregnancy and Nursing Mothers subsections of Kapidex labeling. Kapidex (dexlansoprazole), a proton pump inhibitor (PPI) is the R-enantiomer of lansoprazole, and is indicated for: healing of all grades of erosive esophagitis (EE); maintaining healing of EE (b) (4); and, treating heartburn (b) (4) associated with non-erosive gastroesophageal reflux disease (GERD). (4)

This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Kapidex labeling.

SUBMITTED MATERIAL

Sponsors Proposed Pregnancy and Nursing Mothers Labeling for Kapidex.

Highlights

No information.

8.1 Pregnancy

(b) (4)

(b)

(b) (4)

8.3 Nursing Mothers

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from dexlansoprazole and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

RECOMMENDATIONS

Provided below are MHT's recommended revisions to the sponsors' proposed labeling. Appendix A of this review provides a track changes version of labeling that highlights all changes made.

Highlights

-----USE IN SPECIFIC POPULATIONS-----

(b) (4)

8.1 Pregnancy

Teratogenic effects

Pregnancy Category B. There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, Kapidex should be used during pregnancy only if clearly needed.

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately 9 times the maximum recommended human dose ([60 mg] based on body surface area [BSA]) revealed no evidence of harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 40 times the recommended human dose (based on BSA) and pregnant rabbits at oral lansoprazole doses up to 16 times the recommended human dose (based on BSA) revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

MHT Comment:

1. *Section reorganized to provide the summary statement of the most clinically relevant bottom line based on the available data.*
2. *If the Division feels that the actual (rather than relative) animal doses should be included in the label, please include these details in a subsection titled 13.3 Reproductive Toxicology. While this data may be important for future reference or for those conducting translational research, it is not clinically relevant for prescribers and therefore, should not be subsection 8.1 Pregnancy.*

8.3 Nursing Mothers

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies [see *Carcinogenesis, Mutagenesis, Impairment of Fertility, (13.1)*], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

MHT Comment: Refer to 21 CFR 201.57(c) (9)(iii)(C) 8.3 Nursing Mothers for basis if needed.

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for Kapidex is provided on pages 3-4 of this review. Appendix A of this review also provides a track changes version of labeling.

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Appendix A –
Track Changes Version of Labeling

15 Page(s) Withheld

 Trade Secret / Confidential (b4)

 √ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

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DRUG SAFETY OFFICE REVIEWER

Karen Feibus
1/13/2009 02:56:18 PM
MEDICAL OFFICER
I have reviewed this document and concur with the
recommendations and conclusions.

Lisa Mathis
1/16/2009 02:18:54 PM
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 22, 2008

To: Donna Griebel, M.D.
Director, Division of Gastroenterology Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, Pharm.D., Deputy Director
Division of Medication Error Prevention and Analysis

From: Deveronne Hamilton-Stokes, RN, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Labeling Review for (b)

Drug Name(s): (Dexlansoprazole) Delayed-Release Capsules
30 mg, 60 mg, (b) (4)

Application Type/Number: NDA 22-287

Applicant: TAP Pharmaceuticals Inc.

OSE RCM #: 2008-1281

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis noted areas of vulnerability that could lead to medication errors with the container labels and carton labeling of (b) (4). Improvements that could be made include further differentiating the product strengths from one another, relocating the unit of measurement to appear beside the numerical portion of the strength, decreasing the prominence of the net quantity and including the NDC # on the principle display panel of all labels and labeling.

For full recommendations, we refer you to section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Gastroenterology Products for a review of the labels and labeling of (b) (4).

1.2 REGULATORY HISTORY

The Applicant initially submitted the proposed name (b) (4) for review and comment. However, the Division of Drug Marketing, Advertising, and Communications (DDMAC) objected to the use of this name from a promotional perspective and the Division concurred (see OSE Review 2007-2396 dated December 4, 2007). Subsequently, the Applicant submitted alternate names (b) (4) Kapidex (secondary) for review and comment. (b) (4)
(b) (4)

The trade name review of Kapidex will be forthcoming in a separate review.

1.3 PRODUCT INFORMATION

(b) (4) (dexlansoprazole) is a proton pump inhibitor indicated for healing (b) (4) of all grades of erosive esophagitis (EE), maintaining healing of erosive esophagitis (b) (4) and treating (b) (4) heartburn (b) (4) associated with gastroesophageal reflux disease (GERD). The recommended dose for healing of EE is 60 mg (b) (4) once daily for up to 8 weeks. The recommended dose for maintenance of healed EE is 30 mg (b) (4), once daily. The recommended dose for symptomatic GERD is 30 mg, once daily for 4 weeks. The product will be available as 30 mg, 60 mg (b) (4) capsules. All strengths will be supplied in unit dose packages of 100 and bottles of 30 count, 90 count, and 1000 count.

2 METHODS AND MATERIALS

This section describes the methods and materials used by our medication error staff to conduct a label, labeling and/or packaging risk assessment (see Section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because The Division of Medication Error Prevention and Analysis staff analyzes reported misuse of drugs, we are able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. We use Failure Modes and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

For this product, the Applicant submitted on March 7, 2008, the following labels and labeling for our review (see Appendix A, B, C, D, E, F, G, H, and I):

- Container Label (30 count, 90 count, and 1000 count): 30 mg, 60 mg, (b) (4)
- Hospital Unit Dose Blister: 30 mg, 60 mg, (b) (4)
- Hospital Unit Dose Carton Labeling (100 count): 30 mg, 60 mg, (b) (4)
- Professional Sample Blister Card (5 count): 30 mg, 60 mg (b) (4)
- Professional Sample Blister Tray (5 x 5 count): 30 mg, 60 mg (b) (4)
- Professional Sample Container Label (7 count): 30 mg, 60 mg, (b) (4)
- Professional Sample Container Label (30 count): 60 mg (b) (4)
- Package Insert Labeling (no image)

3 RESULTS

Upon review of the labels and labeling, the Division of Medication Error Prevention and Analysis noted several vulnerabilities that may contribute to medication errors.

3.1 ALL LABELS AND LABELING

The colors blue and green which are utilized for the trade and established names are also utilized as part of the trade dress for the 60 mg (blue) (b) (4). Furthermore, all of the strengths are presented in the same black font color.

The unit of measurement (i.e., mg) appears beneath the numerical portion of the product strength.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.2 CONTAINER LABELS (30 COUNT, 90 COUNT, AND 1000 COUNT)

The net quantity is bold and appears to be highlighted because it is located in a color stripe.

The NDC number is not readily visible as it does not appear on the principle display panel, which is not in accordance with 21 CFR 207.35(b)(3)(i).

3.3 PROFESSIONAL SAMPLE BLISTER CARD (5 COUNT)

The principle display panels for all 3 strengths appear almost identical because the same green color is presented on the majority of the principle display panel. The only difference is the top corners are presented in different colors, which is not enough to differentiate the strengths.

The product strength does not appear in conjunction with the trade name and the established name on the panels which contain the blister.

The 'mg' content of each capsule is not clearly communicated.

3.4 PROFESSIONAL SAMPLE CONTAINER LABEL (7 COUNT)

The principle display panels for all 3 strengths appear almost identical because the same green color is presented on the majority of the principle display panel. The only difference is the top corners are presented in different colors, which is not enough to differentiate the strengths.

The statement "Professional Sample-Not for Sale" does not appear on the principle display panel of the 7 count container label; however, it is prominently displayed at the top of the principle display panel on the 30 count.

The NDC number is not readily visible as it does not appear on the principle display panel, which is not in accordance with 21 CFR 207.35(b)(3)(i).

3.5 PROFESSIONAL SAMPLE CONTAINER LABEL (30 COUNT)

The net quantity is bold and appears to be highlighted because it is located in a color stripe.

The NDC number is not readily visible as it does not appear on the principle display panel, which is not in accordance with 21 CFR 207.35(b)(3)(i).

3.6 INSERT LABELING

No Comments

4 DISCUSSION

Our evaluation of the labels and labeling, noted several areas of needed improvement.

4.1 ALL LABELS AND LABELING

Our review noted concerns with the use of identical and overlapping colors appearing on all of the strengths. Because the colors that the Applicant has selected for the proprietary name (green) and the established name (blue) are also colors utilized as part of the trade dress to differentiate the strengths, all of the labels and labeling appear similar. Using the same blue and green color on all the labels and labeling contributes to their similarity and diminishes the usefulness of color for product strength differentiation. Additionally, the numerical portions of all of the strengths are presented in the same black color font which further contributes to the labels and labeling looking alike. Based on postmarketing experience, labels and labeling that are not adequately differentiated increase the risk of confusion and also contribute to product selection errors that can lead to an over or under dose because the wrong strength is dispensed and administered.

The unit of measurement appears beneath the numerical portion of the product strength. This location is not the usual placement. Without the unit of measurement (mg) appearing beside the numerical portion of the product strength, the strength could look like the net quantity and lead to confusion, especially since the net quantity (30 **(b) (4)**) overlaps with the strengths (30 mg **(b) (4)**)

4.2 CONTAINER LABELS (30 COUNT, 90 COUNT, AND 1000 COUNT)

The net quantity is as prominent as the strength because it appears bolded in a color bar which overemphasizes this information and distracts attention away from the product strength. This presentation increases the risk that the net quantity may be confused as the product strength, especially due to the fact that the net quantity (30 **(b) (4)**) overlaps with the strengths (30 mg **(b) (4)**)

4.3 PROFESSIONAL SAMPLE BLISTER CARD (5 COUNT)

Three-quarters of the principle display panel of all of the strengths appear in the same green font color which increases the similar appearance of the labels. The minimal differences in the presentation of the strength may not afford adequate differentiation. Look-alike labels/labeling with similar color schemes may lead to product selection errors especially in physicians offices where they will be stored.

We also noted that the product strength does not appear with the proprietary name and established name on the panels which contain the blisters. If this portion becomes detached, there will not be a statement of strength presented for patients. Additionally, the presentation of the name and strength should still remain present/intact when patients remove a capsule from the blister card.

In its current presentation, the 'mg' content of each capsule could be misunderstood or overlooked causing patients to take the entire contents of the blister card as a single dose.

4.4 PROFESSIONAL SAMPLE CONTAINER LABEL (7 COUNT)

Three-quarters of the principle display panel of all of the strengths appear in the same green font color which increases the similar appearance of the labels. The minimal differences in the presentation of the strength may not afford adequate differentiation. Look-alike labels/labeling with similar color schemes may lead to product selection errors.

4.5 PROFESSIONAL SAMPLE CONTAINER LABEL (30 COUNT)

The net quantity is as prominent as the strength because it appears bolded in a color bar which overemphasizes this information and distracts attention away from the product strength. This presentation increases the risk that the net quantity may be confused as the product strength, especially due to the fact that the net quantity **(b) (4)** overlaps with the strengths **(b) (4)**

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and layout design of the proposed labels and labeling introduce vulnerability to confusion that could lead to medication errors with **(b) (4)**. The risks we have identified can be addressed and mitigated prior to approval. Recommendations are provided below in Section 5.2.

5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling we have identified areas of needed improvement. We have provided recommendations in section 5.2 below and request that they be forwarded to the Applicant for implementation prior to approval of this application.

The Division of Medication Error Prevention and Analysis would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any correspondence to the Applicant pertaining to this issue. If you have further questions or need clarification, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

5.2.1 All Labels and Labeling

1. Since the colors selected for the proprietary name (green) and the established name (blue) are also colors utilized as part of the trade dress to differentiate the strengths, all of the labels and labeling appear similar. Using the same blue and green color on all the labels and labeling contributes to their similarity and diminishes the usefulness of color for product strength differentiation. Additionally, the numerical portions of all of the strengths are presented in the same black color font which further contributes to the labels and labeling looking alike. Revise the colors of the proprietary name and established names so they do not overlap with any of the colors used to differentiate the strengths. Additionally, distinguish the numerical portions of the strengths with the use of colors, shading, boxing or some other means. This will also minimize the similarity of the strength and net quantity.
2. Ensure the unit of measurement (mg) appears to the immediate right of the strength, since this is the location that practitioners and patients are accustomed to finding it when reading from left to right.

5.2.2 Container Labels (30 count, 90 count, and 1000 count)

1. Debold the net quantity and remove the colored strip from the net quantity and RX only statement which will lessen the potential for the net quantity to be confused with the strengths since the 30 **(b) (4)** quantities overlap with the 30 mg **(b) (4)** strengths. In revising the appearance of the net quantity, maximize the distance between the strength and the net quantity.
2. Relocate the NDC number to the top one-third of the principle display panel, to be in accordance with 21 CFR 207.35(b)(3)(i).

5.2.3 Professional Sample Blister Card (5 count)

1. As currently presented, the identical color (green) is used on the majority of the principle display panel for all three strengths. Revise the colors of the principle display panel so that they are undoubtedly distinguishable from one another and the colors do not overlap.
2. Include the product strength in conjunction with the proprietary name and established names on the panels which contain the blisters. Additionally, ensure this information remains present/intact when the capsules are removed from the blister.
3. Revise to include the statement: "Each capsule contains XX mg" so that patients will know that the entire blister card is not equivalent to 30 mg, 60 mg **(b) (4)**. Ensure this statement is prominently displayed.

5.2.4 Professional Sample Container Label (7 count)

1. As currently presented, the identical color (green) is used on the majority of the principle display panel for all three strengths. Revise the colors of the principle display panel so that they are undoubtedly distinguishable from one another and the colors do not overlap.
2. Relocate the statement “Professional Sample-Not for Sale” to the principle display panel, as it is presented on the sample 30 count container.
3. Relocate the NDC number to the top one-third of the principle display panel, to be in accordance with 21 CFR 207.35(b)(3)(i).

5.2.5 Professional Sample Container Label (30 count)

1. Debold the net quantity and remove the colored strip from the net quantity and RX only statement which will lessen the potential for the net quantity to be confused with the strengths since the 30**(b) (4)** quantities overlap with the 30 mg**(b) (4)** strengths. In revising the appearance of the net quantity, maximize the distance between the strength and the net quantity.
2. Relocate the NDC number to the top one-third of the principle display panel, to be in accordance with 21 CFR 207.35(b)(3)(i).

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 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

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M E M O R A N D U M

Date: August 2, 2008

From: Amy M. Taylor, MD, MHS, Medical Officer
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Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Donna Griebel, MD, Director
Division of Gastroenterology Products

Re: PREA requirement for dexlansoprazole NDA 22-287

Sponsor: TAP Pharmaceutical Products Inc. / Takeda

Drug: Dexlansoprazole

Indications (proposed): Adult:
Healing (b) (4) of all grades of erosive
esophagitis (EE)

Maintaining healing of EE (b) (4)

Treating (b) (4) heartburn (b) (4)
(b) (4) associated with gastroesophageal reflux disease
(GERD)

Dosage form and

route of administration: 30 mg , 60 mg, (b) (4) oral delayed release capsules

Dosing regimen:

Healing of EE: 60 mg (b) (4) once daily for up to 8 weeks

Maintenance of Healed EE: 30 mg (b) (4) once daily.
(b) (4)

Symptomatic GERD: 30 mg once daily for 4 weeks

Document ID Number:

NDA 22-287 CDER Stamp Date: 12/28/07

Consult Questions:

- 1) The Division of Gastroenterology Products (DGP) requests assistance to determine whether there is pediatric interest in dexlansoprazole.
- 2) DGP requests input in determining if NDA 22-287 for dexlansoprazole triggers PREA because of a possible new indication for the treatment of nighttime GERD.

Background

In December 2007, TAP Pharmaceuticals submitted an NDA for dexlansoprazole for the healing of erosive esophagitis, maintenance of healing of EE, and treatment of symptomatic GERD. In the NDA submission, the Sponsor requested a deferral of pediatric studies required under the Pediatric Research Equity Act (PREA) for patients ages 1 month to 17 years and a waiver for patients aged 0 to 1 month.

The reason for the deferral request is that adult studies are completed and ready for approval. The rationale for the waiver in pediatric patients ages 0 to 1 month is that the necessary studies in this age group are impossible or highly impractical. The Sponsor cites the North American Society for Pediatric Gastroenterology and Nutrition (NASPGHAN) guidelines for the evaluation and treatment of gastroesophageal reflux in infants and children. These guidelines recommend a non-pharmacologic approach, a two week conservative GERD management prior to the initiation of pharmacologic treatment. Therefore, the Sponsor concludes, treatment of GERD in neonates is considered impractical in that by the time the GERD is recognized, diagnosed and non-pharmacologic treatment is attempted to alleviate the condition, the newborn will be greater than 1 month of age.

The Sponsor submitted a plan for pediatric studies in October 2006.

Drug and Proposed Indication

Dexlansoprazole has not been approved for marketing. The current NDA submission is for an oral delayed-release capsule in 30 mg, 60 mg (b) (4) strength.

Dexlansoprazole is a substituted benzimidazole that inhibits gastric acid secretion. It is the R-enantiomer of lansoprazole a proton pump inhibitor (PPI). According to the consult from DGP, dexlansoprazole is not considered the same active ingredient or active moiety as lansoprazole, but is the same as one of the active moieties that constitute lansoprazole.

Reviewer's comment: PMHS requested that the Office of the Chief Counsel weigh in on the question of whether an enantiomer of an active ingredient is considered a new active ingredient under PREA. OCC has determined that an enantiomer is considered to be a new active ingredient and therefore triggers PREA.

Gastroesophageal reflux disease (GERD) is defined as symptoms or complications of gastroesophageal reflux (GER). Common presenting symptoms of GERD differ depending on the age of the child. In infants and young children, GERD symptoms include recurrent vomiting, poor weight gain, irritability, dysphagia or feeding refusal, and respiratory complications. Older children present with heartburn, regurgitation, and dysphagia. GERD is typically diagnosed based on history and physical examination supplemented by endoscopy to check for esophagitis. Treatment of GERD includes lifestyle changes, pharmacotherapy and surgical treatment. Antacids, histamine-2 receptor inhibitors, and PPIs have been used to treat GERD.¹

The Sponsor is seeking approval of the use of dexlansoprazole for healing (b) (4) of all grades of erosive esophagitis (EE), maintaining healing of EE (b) (4), and treating (b) (4) heartburn (b) (4) associated with gastroesophageal reflux disease (GERD) in adults. (b) (4)

Reviewer's comment: (b) (4)

Lansoprazole is approved for the short-term treatment of GERD and erosive esophagitis in pediatric patients aged 1 to 17 years. (b) (4)

However, other elements in the dexlansoprazole application trigger PREA, namely the new active ingredient.

¹ Michail S. Gastroesophageal reflux. *Pediatr in Rev* 2007;28:101-110

Pediatric Written Requests and Labeling for Currently Available PPIs

The FDA issued similar Written Requests (WR) for all five currently marketed PPIs. Pediatric exclusivity has been granted for omeprazole and lansoprazole. The others are at various stages of submitting a complete response. Some have submitted partial responses and received approval of updated labeling (i.e. lansoprazole, omeprazole and esomeprazole). Thus far, no products have received approved indications in patients under 1 year. Lansoprazole was studied in patients 1 month to 11 months, but according to the Sponsor, efficacy was not established. The study report is still under review by DGP.

A number of proton-pump inhibitors are approved for marketing in the U.S. The following PPIs have indications approved, pediatric studies under review, or ongoing development programs for the pediatric population.

Prevacid[®] (lansoprazole) – WR issued 8/26/99; last amendment 9/6/05; exclusivity granted 7/15/08. Lansoprazole is approved for use in pediatric patients aged 1 to 17 years for the short-term treatment of GERD and erosive esophagitis.

Prilosec[®] (omeprazole) – WR issued 7/1/99; last amendment 11/2/00; exclusivity granted 5/1/01. Omeprazole is approved for use in pediatric patients aged 1 to 16 years for treatment of acid-related gastrointestinal disease, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis. The OTC product of Prilosec is not approved for use in pediatric populations.

Nexium[®] (esomeprazole) – WR issued 12/31/01; last amendment 3/29/07. Esomeprazole is approved for use in pediatric patients aged 1 to 17 years for short-term treatment of GERD and in pediatric patients aged 1 to 11 years for healing of erosive esophagitis.

Protonix[®] (pantoprazole) – WR 12/31/01; last amendment 5/17/07. Pantoprazole has no approved uses in the pediatric population. ^{(b) (4)}

Aciphex[®] (rabeprazole) – WR issued 12/31/01; last amendment 6/27/07. Rabeprazole is approved for use in pediatric patients 12 years and above for short-term treatment of GERD.

Reviewer comment: At the time of the exclusivity determination for lansoprazole, the Board noted that the clinical study in patients 1 month to 11 months may not have shown an effect because the study was not powered to do so. The reasons for the failure to demonstrate efficacy may be clarified during the ongoing review of the complete response to the WR. In addition, questions were raised as to whether the primary endpoint of the study could determine a clinically meaningful treatment effect. The

primary endpoint of the study focused on the reduction of crying/fussing/irritability episodes during feeding. A more sensitive endpoint may be needed such as the relationship between acid suppression and weight gain.

PREA Requirements

The Pediatric Research Equity Act of 2007 (PREA) requires pediatric studies with all products approved under section 505 in which there is a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. The requirement for pediatric studies can be waived if one or more applies:

- 1) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed)
- 2) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups
- 3) The drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.
- 4) Reasonable attempts to produce an age appropriate formulation have failed. This process must be documented.

Furthermore, if a waiver is granted based on evidence the drug is unsafe or ineffective in the pediatric population, the information must appear in the product labeling.

Pediatric studies can be deferred in all pediatric age groups or in a subgroup if one or more applies:

- 1) the drug or biological product is ready for approval for use in adults before pediatric studies are complete
- 2) pediatric studies should be delayed until additional safety or effectiveness data have been collected
- 3) there is another appropriate reason for deferral

If studies are deferred, the Sponsor must submit:

- 1) A description of the planned or ongoing Studies;
- 2) Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and
- 3) A timeline for the completion of such studies.

All waivers and deferrals must be reviewed by the Pediatric Review Committee before approval of applications.

Answers to Consult Questions

- 1) The Division of Gastroenterology Products (DGP) requests assistance to determine whether there is pediatric interest in dexlansoprazole.

Dexlansoprazole will be the sixth PPI product to be marketed if approved. Since none of the other PPI's is approved in patients less than 1 year of age, conducting pediatric studies with the drug would represent a therapeutic benefit over the other PPIs. For older age groups, a new PPI may not represent a therapeutic benefit per se, unless the agent possesses a better safety profile or affords easier dosing. Nonetheless, dosing and safety information would still be needed to appropriately label the drug. Moreover, under PREA, in addition to the drug not representing a meaningful therapeutic benefit, the drug must not be expected to be used in a substantial number of pediatric patients. Predicting prior to marketing how much a drug will be used is difficult. PPIs, as a class, are used frequently in the pediatric population.

Presuming no safety concerns arise as the NDA review is finalized, because there is, currently, limited knowledge of the safety and effectiveness of the PPIs in pediatric patients under 1 year of age, consideration should be given to issuing a WR for dexlansoprazole for this pediatric age group. Since the study of lansoprazole in patients less than one year did not demonstrate effectiveness, a different endpoint and/or study design is likely to be required.

2) (b) (4)

(b) (4)

Regardless, since dexlansoprazole, as an enantiomer of lansoprazole, is considered to be a new active ingredient, PREA is triggered. Pediatric studies are required unless waived.

A waiver can be granted under PREA if the studies are impossible or impracticable, there is strong evidence that the drug would be unsafe or ineffective in the pediatric population or if the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. The first criterion does not apply. GERD is common in pediatric patients and has been successfully studied in other PPI products. The second criterion (concerns regarding safety or lack of efficacy) would depend on the results of the review of dexlansoprazole currently underway by DGP.

All waivers and deferrals must be reviewed by the PeRC before approval of applications. A pediatric plan must be submitted at the time a deferral is granted.

Additional comments regarding issuing a WR:

(b) (5)

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