PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 208,056
Supporting document/s: 1
Applicant's letter date: March 26, 2015
CDER stamp date: March 26, 2015
Product: Dexilant SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets
Indication: maintenance of healed EE and relief of heartburn; symptomatic non-erosive GERD
Applicant: Takeda Pharmaceuticals, USA Inc.
Review Division: Gastroenterology and Inborn Errors Products
Reviewer: Ke Zhang, PhD
Supervisor/Team Leader: David B. Joseph, PhD
Division Director: Donna Griebel, MD
Project Manager: Maureen Dewey

Template Version: September 1, 2010

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1. Executive Summary

1.1 Introduction

The Sponsor has developed a 30 mg dexlansoprazole delayed-release orally disintegrating (OD) tablet (Dexilant SoluTab). The tablets have been designed to disintegrate in the mouth without chewing or swallowing with water. The OD formulation uses the same active ingredient, dexlansoprazole, as in Dexilant delayed-release capsules.

1.2 Brief Discussion of Nonclinical Findings

A dexlansoprazole degradation impurity has been detected in the drug product in long-term stability samples. See section 2.5 for a brief summary of the safety assessment of the proposed limit for

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, there are no approvability issues.

1.3.2 Additional Nonclinical Recommendations

Recommendations for labeling changes are shown below.

1.3.3 Labeling

The current Dexilant label, revised on December 19, 2014 under NDA 22,287 (S-019), serves as the basis for the proposed label. The Sponsor submitted the proposed label with no changes in the nonclinical data (subsections 8.1, 8.2, 13.1, and 13.2). Our recommendations for the nonclinical parts of the label are shown below.

Sponsor’s Proposed Version:

8.1. Pregnancy
Recommended Version:

8.1. Pregnancy

Risk Summary
There are no studies with dexlansoprazole use in pregnant women to inform a drug-associated risk. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral dexlansoprazole to rabbits during organogenesis at doses up to 9 times the maximum recommended human dose (MRHD) (based on body surface area) or with administration of oral lansoprazole to rats and rabbits during organogenesis at doses up to 40 and 16 times the MRHD (based on body surface area), respectively [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data
An embryo-fetal development study conducted in rabbits at oral dexlansoprazole doses up to 30 mg/kg/day (approximately nine times the maximum recommended human dexlansoprazole dose [60 mg/day] based on body surface area) during organogenesis showed no effects on fetuses due to dexlansoprazole. In addition, embryo-fetal development studies performed in rats with oral lansoprazole at doses up to 150 mg/kg/day (40 times the recommended human lansoprazole dose based on body surface area) during organogenesis and in rabbits with oral lansoprazole at doses up to
30 mg/kg/day (16 times the recommended human lansoprazole dose based on body surface area) during organogenesis revealed no effects on fetuses due to lansoprazole.

Sponsor’s Proposed Version:

8.2 Lactation

Risk Summary
There is no information regarding the presence of dexlansoprazole in human milk, the effects on the breastfed infant, or the effects on milk production. However, lansoprazole and its metabolites are present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for dexlansoprazole and any potential adverse effects on the breastfed child from dexlansoprazole or from the underlying maternal condition.

Data
Animal Data
When $^{14}$C lansoprazole was administered orally at 2 mg/kg to lactating rats 14 days after parturition, milk collected at 0.5, 2 and 6 hours after the lansoprazole dose contained 2- to 6-fold higher concentrations of radioactivity than plasma. Almost all of the radioactivity was determined to be from lansoprazole metabolites.

Evaluation: The information from the cited animal studies in subsection 8.2 is acceptable. There is one incorrect spelling in the sponsor’s version ("radioactivity"), which should be changed to “radioactivity”.

Recommended Version:

Risk Summary
There is no information regarding the presence of dexlansoprazole in human milk, the effects on the breastfed infant, or the effects on milk production. However, lansoprazole and its metabolites are present in rat milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DEXILANT and any potential adverse effects on the breastfed child from DEXILANT or from the underlying maternal condition.

Data
When $^{14}$C lansoprazole was administered orally at 2 mg/kg to lactating rats 14 days after parturition, milk collected at 0.5, 2 and 6 hours after the lansoprazole dose contained 2- to 6-fold higher concentrations of radioactivity than plasma. Almost all of the radioactivity was determined to be from lansoprazole metabolites.
Sponsor’s Proposed Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg/kg/day, about one to 40 times the exposure on a body surface (mg/m²) basis of a 50 kg person of average height [1.46 m² body surface area (BSA)] given the recommended human dose of lansoprazole 30 mg/day.

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats [see Clinical Pharmacology (12.2)].

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human lansoprazole dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In a 24 month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg/kg/day, two to 80 times the recommended human lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole/kg/day (40 to 80 times the recommended human lansoprazole dose based on BSA) and female mice treated with 150 to 600 mg lansoprazole/kg/day (20 to 80 times the recommended human lansoprazole dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human lansoprazole dose based on BSA).

A 26 week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.

Lansoprazole was positive in the Ames test and the in vitro human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, the in vivo mouse micronucleus test or the rat bone marrow cell chromosomal aberration test.

Dexlansoprazole was positive in the Ames test and in the in vitro chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the in vivo mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.
Evaluation: No revision is needed for subsection 13.1, since it is identical to that in the current approved label.

Sponsor’s Proposed Version:

2 Drug Information

2.1 Drug

Trade Name: Dexilant SoluTab (dextransoprazole)

Code Name: TAK-390

Chemical Name:

(+)-2-[(R)-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methyl] sulfinyl]-1H-benzimidazole

Molecular Formula: C_{16}H_{14}F_{3}N_{3}O_{2}S

Molecular Weight: 369.36

Structure or Biochemical Description:
Pharmacologic Class: proton pump inhibitor

2.2 Relevant INDs, NDAs, and DMFs: IND 106,858, NDA 22,287, NDA 20,406, DMF (b)(4) DMF (b)(4)

2.3 Drug Formulation

DEXILANT delayed-release capsules are available in two dosage strengths: 30 mg and 60 mg per capsule. The Sponsor has developed a 30 mg dexlansoprazole delayed-release orally disintegrating (OD) tablet (Dexilant SoluTab). The tablets have been designed to disintegrate in the mouth without chewing or swallowing with water. The OD formulation uses the same active ingredient, dexlansoprazole, as in Dexilant delayed-release capsules.

The formulation ingredients are listed in the Sponsor’s tables below. Dexlansoprazole delayed-release orally disintegrating tablets are comprised of:

- enteric coated microgranules (b)(4)
- dexlansoprazole coated microgranules (b)(4)

Table 1.a shows the composition of the dexlansoprazole OD tablets whose compositions are shown in the Sponsor’s tables below.

The composition of the final dexlansoprazole OD tablets is shown in Table 1.e.
2.4 Comments on Novel Excipients

For most of the excipients, the daily intake at the proposed maximum dose (2 OD tablets/day) is not higher than the daily intake from other approved oral formulations based on the FDA inactive ingredient databases. The excipient “strawberry dumarome” is not found in the FDA inactive ingredient databases, but it is likely listed as “flavor strawberry” or “strawberry” in the databases. A summary of the supporting safety information is provided below.

The excipient methylacrylate methacrylate methacrylic acid copolymer (listed under a different name in the FDA inactive ingredient databases) has been used in only two approved drug products, and at lower amounts. Since the maximum daily dose of methylacrylate methacrylate methacrylic acid copolymer from the approved oral drug products is lower than the dose from the proposed maximum daily dose of Dexilant SoluTab, nonclinical data is needed to assess the safety of this excipient (see below).
Strawberry Durarome:

The information described below was provided in DMF (amendment dated May 18, 2011) or in IND 106,858 (amendment dated July 21, 2014). The sponsor provided a letter of authorization for DMF in this application.

Dexilant SoluTab contains mg strawberry durarome per tablet, resulting in a maximum daily intake of mg at the proposed maximum dose. The composition of this flavoring product is described in DMF. Strawberry durarome contains as the major ingredients (greater than 40% but less than 50% of total product for each) each have a GRAS designation for (21 CFR 184.1444 and 184.1854, respectively).

Strawberry durarome also contains other ingredients, most of which have a GRAS designation. The other ingredients include

Therefore, two OD tablets contain

Strawberry durarome is also used in which is approved for use (information provided by Sponsor in IND 106,858, amendment dated July 21, 2014). Based on the maximum recommended dose of the maximum daily intake of strawberry durarome The Sponsor stated that strawberry durarome has been used commonly in food products.

Reference ID: 3864324
Based on the information described above for the individual ingredients in strawberry durarome, and the proposed maximum dose of two tablets per day, there are no safety concerns about the use of this flavoring product in dexilsoprazole OD tablets.

Methylacrylate methylmethacrylate methacrylic acid copolymer:

Methylacrylate methylmethacrylate methacrylic acid copolymer
copolymer. The supporting nonclinical data for (b)(4) is contained in DMF (b)(4) (a letter of authorization was provided in this application). A summary of the major findings in the nonclinical data, followed by a safety assessment of the maximum dose of (b)(4) from Dexilant SoluTab is provided below.

A distribution/excretion study was conducted in rats using oral administration of unlabeled (b)(4) methylacrylate copolymer (600 mg/kg/day) for 13 days, followed by administration of 14C methacrylic copolymer (600 mg/kg, 10 μCi) on day 14. The highest concentration of radioactivity in tissues was found in the cecum wall of the animals sacrificed at 24 and 72 hours following administration of the radiolabeled dose, with the maximum concentration of radioactivity occurring at 24 hours. Low levels of radioactivity were found in colon wall, duodenum wall, ileum, mesenteric lymph nodes, stomach, and esophagus. The excretion data showed that radioactive material was excreted entirely in feces, based on collection of urine and feces for 10 days. The presence of radioactivity in the GI tract was likely indicative of adsorption rather than absorption. The distribution and excretion data suggest that (b)(4) methacrylate copolymer (b)(4) is very poorly absorbed from the gastrointestinal tract in rats. However, it should be noted that collection of blood and tissue samples was limited to the time-points of 24 hr, 72 hr, and 10 days post-dose, therefore the study data did not provide information about absorption prior to 24 hr post-dose.

In a 28-day oral toxicity study with (b)(4) methacrylate copolymer in dogs, doses of 0 (empty gelatin capsules), 100, 200, and 400 mg/kg/day were tested (oral capsules, 3 dogs/sex/group). The high-dose of 400 mg/kg/day was the NOAEL.

In a 26-week oral toxicity study with (b)(4) methacrylate copolymer in rats, doses of 0 (vehicle control), 200, 500 and 1500 mg/kg/day were tested (oral gavage, 15 rats/sex/group). The high-dose of 1500 mg/kg/day was the NOAEL.

In a reproductive toxicity study with (b)(4) methacrylate copolymer in rats, the animals were treated by oral gavage during gestation days 5 to 19 at doses of 0 (0.5% sodium-carboxymethylcellulose aqueous solution) and 1000 mg/kg/day. The dose of 1000 mg/kg/day was the NOAEL for both dams and fetuses.

(b)(4) methacrylate copolymer tested negative in the Ames test, L5178Y TK+- mouse lymphoma test, chromosomal aberration test in human lymphocytes, and the in vivo mouse micronucleus assay.
The amount of [redacted] in dextra\(\text{lsoprazole OD tablets is [redacted]} \text{ mg/tablet. Therefore the maximum daily dose will be [redacted]} \text{ mg at the proposed maximum dose of two OD tablets (60 mg dexla}\text{soprazole/day for up to eight weeks). The target patient populations for this application are limited to adults only, although clinical trials with Dexilant SoluTab in pediatric patients are planned and/or in progress. The maximum daily dose of [redacted] (approximately [redacted] mg/kg based on a 60-kg body weight) is much less than the NOAEL (1500 mg/kg/day) identified in the 26-week oral toxicity study in rats. The NOAEL provides a safety margin of [redacted]-fold based on a mg/kg comparison to the maximum dose in adults, with the assumption of minimal or no systemic absorption. Therefore, for the proposed use in adults, there are no safety concerns about [redacted] contained in dextra\(\text{lsoprazole OD tablets. Given the high safety margin from the rat NOAEL in the 26-week study relative to the adult dose, and the absence of toxicity at any dose tested in the 26-week rat and 28-day dog studies, it appears that the overall toxicity data can support the higher doses (mg/kg) of [redacted] that will occur when young pediatric patients are administered with dextra\(\text{lsoprazole OD tablets in clinical trials.}

2.5 Comments on Impurities/Degradants of Concern

A degradation impurity, [redacted] was detected in the drug product in long-term stability samples. [redacted] The safety of this impurity was evaluated in this review. The applicable qualification threshold for the impurity [redacted] would allow for a maximum daily intake of [redacted] mcg as recommended by ICH Q3B(R2), or approximately [redacted] mg/kg/day if a 60-kg body weight is assumed. The maximum potential daily dose of impurity [redacted] at the proposed limit of [redacted] % is [redacted] mcg ( [redacted] mg/kg/day based on an assumed bodyweight of 60 kg), based on the maximum proposed clinical dose of 60 mg (2 x 30 mg) for DEXILANT SoluTab. Since the maximum potential daily intake of [redacted] mcg/day) exceeds the ICH qualification threshold [redacted] mcg/day) at the proposed limit, a toxicity study to support qualification was needed. In a 4-week oral toxicity study in rats, the dose of [redacted] mg/kg/day of impurity [redacted] (human equivalent dose = [redacted] mg/kg/day) was well tolerated. This dose is approximately 10 times the maximum potential daily dose at the proposed limit of [redacted]%. Therefore, impurity [redacted] is considered to be qualified at [redacted] %.

2.6 Proposed Clinical Population and Dosing Regimen

DEXILANT SoluTab (30 mg strength) is indicated for [redacted] maintenance of healing of EE and relief of heartburn for up to six months (30 mg/day), and treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks (30 mg/day). The indications [redacted]. The patient population for both DEXILANT formulations is limited to adults.
2.7 Regulatory Background

Dexlansoprazole is the R-enantiomer of the racemate lansoprazole, a proton pump inhibitor (PPI). Both dexlansoprazole and lansoprazole are approved drugs in the U.S. The Sponsor has developed a 30 mg dexlansoprazole delayed-release orally disintegrating tablet (IND 106,858), with the trade name Dexilant SoluTab. The tablets are designed to disintegrate in the mouth without chewing or swallowing with water. The OD formulation uses the same active pharmaceutical ingredient, dexlansoprazole, as in Dextilant delayed-release capsules.

The Division of Gastroenterology and Inborn Errors Products provided written responses to the Sponsor on February 13, 2015, for a pre-NDA meeting (IND 106,858). In the written responses, a nonclinical question about an impurity, \( \text{(b)(4)} \), was discussed. The Sponsor proposed \( \text{(b)(4)} \).

We provided the following response to the Sponsor's proposal and question:

“No, we do not agree with your assessment. Specifically, we do not agree with your conclusion. API (dexlansoprazole) is known to be mutagenic and dexlansoprazole, it is acceptable to control the \( \text{(b)(4)} \) impurity level in Dexlansoprazole Delayed-Release ODT based on the recommendations in ICH guidance Q3B(R2).

We note that the applicable qualification threshold for impurities in your product is \( \text{(b)(4)} \) %, which would allow for a maximum daily intake of \( \text{(b)(4)} \) mcg, as recommended by ICH Q3B(R2). If you propose a limit for \( \text{(b)(4)} \) that allows for exposure greater than \( \text{(b)(4)} \) mcg/day, the qualification of \( \text{(b)(4)} \) would depend on the results of your 4-week toxicity study of TAK-390 and \( \text{(b)(4)} \) in rats.”

The 4-week toxicity study in rats using a fixed dose of dexlansoprazole with and without \( \text{(b)(4)} \) was submitted in this NDA.

3 Studies Submitted

A 4-week oral toxicity study in rats with a fixed dose of dexlansoprazole in the presence and absence of the impurity \( \text{(b)(4)} \).

3.1 Studies Reviewed

The above mentioned 4-week oral toxicity study in rats was reviewed.

3.2 Studies Not Reviewed

None.
3.3 Previous Reviews Referenced
None.

4 Pharmacology
4.1 Primary Pharmacology
N/A

4.2 Secondary Pharmacology
N/A

4.3 Safety Pharmacology
N/A

5 Pharmacokinetics/ADME/Toxicokinetics
N/A

6 General Toxicology
N/A

7 Genetic Toxicology
N/A

8 Carcinogenicity
N/A

9 Reproductive and Developmental Toxicology
N/A

10 Special Toxicology Studies
N/A
Study title: Four-Week Oral Gavage Toxicity Study of TAK-390 in Rats

Study no.: 14-091/SU
Study report location: eCTD # 0000 Module 4.2.3.7.6
Conducting laboratory and location: Drug Safety Research Laboratories
Takeda Pharmaceutical Company Limited
Kanagawa, Japan
Date of study initiation: June 23, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: TAK, Lot B27651-083-31, and 99%

Key Study Findings: TAK-390 (50 mg/kg/day) with and without TAK-390 (mg/kg/day) was tested orally in rats for 4 weeks. Small thymus was seen in the TAK-390 alone group. A decrease in thymus weight was seen in both the TAK-390 alone group and the combination (TAK-390 + TAK-390 ) group. White focus on splenic serosa was observed in both the TAK-390 alone group and the combination group. The histopathological examination revealed minimal eosinophilic change in chief cells in the stomach, minimal to mild hyaline droplets in the renal tubules, and minimal inflammation of the spleen capsule in both the TAK-390 alone group and the combination group. There were no apparent differences in the incidence or severity of the above findings between the TAK-390 alone group and the combination group. The finding in stomach was related to the pharmacological activity of TAK-390 as a proton pump inhibitor. Eosinophilic change in chief cells was also identified in a previous 4-week toxicity study with TAK-390 in rats (00-367/SU).

Methods

Doses: See sponsor's text table 1 below
Frequency of dosing: Daily
Route of administration: Oral gavage
Dose volume: 10 ml/kg
Formulation/Vehicle: 1% w/v hypromellose solution
Species/Strain: Crl:CD(SD) rats
Number/Sex/Group: 10/sex/group
Age: ~6 weeks
Weight: Males: 191-213 g
Females: 146-180 g
Satellite groups: 2/sex/group in controls (group 4), 4/sex/group for treatment (group 5) for toxicokinetics
Unique study design: No
Deviation from study protocol: No deviation occurred which adversely affected the quality of the study.
### Text Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Test Article</th>
<th>Dose (mg/kg/day)</th>
<th>Volume (mL/kg/day)</th>
<th>Conc. (w/v%)</th>
<th>No. of Animals (Animal No.)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>0</td>
<td>10</td>
<td>-</td>
<td>10 (1M001-010)</td>
<td>10</td>
<td>10 (1F001-010)</td>
</tr>
<tr>
<td>2</td>
<td>TAK-390</td>
<td>50</td>
<td>10</td>
<td>0.5</td>
<td>10 (2M001-010)</td>
<td>10</td>
<td>10 (2F001-010)</td>
</tr>
<tr>
<td></td>
<td>TAK-390</td>
<td>50</td>
<td>10</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>TAK-390</td>
<td>+</td>
<td>10</td>
<td>+</td>
<td>10 (3M001-010)</td>
<td>10</td>
<td>10 (3F001-010)</td>
</tr>
<tr>
<td></td>
<td>TAK-390</td>
<td>+</td>
<td>10</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Control</td>
<td>0</td>
<td>10</td>
<td>-</td>
<td>2 (4M001-02)</td>
<td>2</td>
<td>2 (4F001-02)</td>
</tr>
<tr>
<td>5</td>
<td>TAK-390</td>
<td>50</td>
<td>10</td>
<td>0.5</td>
<td>4 (5M001-004)</td>
<td>4</td>
<td>4 (5F001-004)</td>
</tr>
</tbody>
</table>

Control: 1 w/v% hypromellose solution (pH 8 with 0.1-mol/L potassium hydroxide)

A fixed dose of 50 mg/kg/day TAK-390 was tested with and without ***mg/kg/day TAK-390***. The dose of 50 mg/kg/day was selected based on the previous 4-week oral toxicity study in rats (Study No. 00-367/SU). The dose of 50-mg/kg/day is considered by the Sponsor as "the lowest observed adverse effect level" due to a decrease in thymus weight. The dose of ***mg/kg/day TAK-390*** was selected based on the maximum clinical dose of TAK-390 ***mg/kg/day based on a 60-kg bodyweight), adjusting for body surface area, and applying a safety factor of 10.

### Observations and Results

#### Mortality

No deaths were found in this study.

#### Clinical Signs

Salivation was seen in both the TAK-390 alone group and the combination group.

#### Body Weights

There were no treatment-related changes.

#### Feed Consumption

There were no treatment-related changes.

#### Ophthalmoscopy

There were no treatment-related changes.
Hematology

There were no treatment-related changes.

Clinical Chemistry

There were no treatment-related changes.

Urinalysis

There were no clearly treatment-related changes.

Gross Pathology

One male had a small thymus in the TAK-390 alone group. White focus on the splenic serosa was noted in 2 males in the TAK-390 alone group and 1 male in the combination group.

Organ Weights

Decreases in thymus weight in both sexes in the TAK-390 alone group and the combination group were observed. The degree of reduction in thymus weight was comparable between in the TAK-390 alone group and the combination group.

Histopathology

The following histopathological findings were noted: minimal eosinophilic change in chief cells in the stomach (5 males and 3 females in the TAK-390 alone group and 5 males and 2 females in the combination group), minimal to mild hyaline droplets in renal tubules (7 males in the TAK-390 alone group and 8 males in the combination group), and minimal inflammation of the spleen capsule (5 males in the TAK-390 alone group and 2 males in the combination group). There were no apparent differences in incidence or severity of the above findings between the TAK-390 alone group and the combination group. Eosinophilic chief cells in stomach were attributed to the pharmacological activity of TAK-390 as a proton pump inhibitor. The major findings are summarized in the table below (taken from the study report).
**Four-Week Oral Gavage Toxicity Study of TAK-390 in Rats (Study No. 14-091/SU)**

<table>
<thead>
<tr>
<th>Animals</th>
<th>Crl:CD(SD) rats, 6 weeks of age at the start of dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test article</td>
<td>Control¹</td>
</tr>
<tr>
<td>Dose levels (mg/kg/day)</td>
<td>0</td>
</tr>
<tr>
<td>No. of animals (M:F)</td>
<td>10:10</td>
</tr>
<tr>
<td>Mortality (M:F)</td>
<td>0:0</td>
</tr>
<tr>
<td>Gross pathology</td>
<td>-</td>
</tr>
<tr>
<td>Organ weights</td>
<td>-</td>
</tr>
<tr>
<td>Histopathology</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹: 1 w/v% hyromellose solution (pH 8 with 0.1 mol/L potassium hydroxide)

²: The hyaline droplets in the renal tubules were positive for α₂₃₉ globulin in immunohistochemistry.

M: Male, F: Female, -: No test article-related abnormalities, ↓: decrease

**Toxicokinetics**

The plasma concentrations of TAK-390 were determined in the satellite groups after the 1st and 30th doses. The results suggest that \( t_{max} \) for TAK-390 was 0.3 hours. The plasma levels of TAK-390 (\( C_{max} \) and \( AUC_{24hr} \)) were comparable between the 1st and 30th doses and there were no apparent sex differences in any TK parameters. The \( C_{max} \) and \( AUC_{24} \) in the present study were higher than those at the 1st dose in the previous 4-week study in rats, but were similar at the 30th dose. The results are summarized in the Sponsor's text table below.
### Text Table 2

<table>
<thead>
<tr>
<th>Strain</th>
<th>Previous 4-week study</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the start of dosing</td>
<td>Jcl: Wistar 5 weeks</td>
<td>Crl: CD(SD) 6 weeks</td>
</tr>
<tr>
<td>Dose (mg/kg/day)</td>
<td>15 50 150</td>
<td>50</td>
</tr>
<tr>
<td>Volume (mL/kg/day)</td>
<td>5 5 5</td>
<td>10</td>
</tr>
<tr>
<td>Concentration</td>
<td>0.3 1 3</td>
<td>0.5</td>
</tr>
<tr>
<td>Vehicle</td>
<td>5 w/v% gum arabic solution adjusted pH to 6.9-7.1 with 0.1N KOH</td>
<td>1 w/v% hypromellose solution (pH 8 with 0.1 mol/L potassium hydroxide)</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hr)</td>
<td>[0.25:0.25] 0.25:0.25 0.25:0.25 *</td>
<td>[0.3:0.3] 0.67:0.42 0.3:0.3</td>
</tr>
<tr>
<td>* 29th for previous 4-week study and 30th for present study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The concentrations of the test articles (TAK-390 and TAK-390 \[b d\]) in the dosing suspension were analyzed. The results indicated that the mean % of target concentrations were 100% and 104% for TAK-390 and TAK-390 \[b d\], respectively, suggesting that these met the acceptance criteria. The results are presented in the sponsor’s table below.
11 Integrated Summary and Safety Evaluation

Dexlansoprazole is the R-enantiomer of the racemate lansoprazole, a proton pump inhibitor (PPI). Both dexlansoprazole and lansoprazole are approved drugs in the U.S. The Sponsor has developed a 30 mg dexlansoprazole delayed-release orally disintegrating (OD) tablet, with the trade name Dexilant SoluTab. The tablets are designed to disintegrate in the mouth without chewing or swallowing with water. The OD formulation uses the same active ingredient, dexlansoprazole, as in Dexilant delayed-release capsules.

The Division of Gastroenterology and Inborn Errors Products provided written responses to the Sponsor on February 13, 2015, for a pre-NDA meeting (IND 106,858). In the written responses, a nonclinical question about impurity \( \text{(b)(4)} \) in the drug product was discussed. The Sponsor proposed \( \text{(b)(4)} \) The Division concurred with the Sponsor’s proposal. The Sponsor submitted a 4-week toxicity study in rats using a fixed dose of dexlansoprazole with and without \( \text{(b)(4)} \) in this NDA, to support qualification of \( \text{(b)(4)} \).

In the 4-week oral toxicity study in rats, TAK-390 (50 mg/kg/day) with and without TAK-390 \( \text{(b)(4)} \) mg/kg/day) was tested. The study report uses the term “TAK-390 \( \text{(b)(4)} \) instead of \( \text{(b)(4)} \) but these terms represent the same impurity. The histopathological examination revealed minimal eosinophilic change of chief cells in the stomach, minimal to mild hyaline droplets in renal tubules, and minimal inflammation of the spleen capsule in both the TAK-390 alone group and the combination (TAK-390 + \( \text{(b)(4)} \) group. There were no apparent differences in the incidence or severity in the above findings between the TAK-390 alone group and the combination group. The finding in stomach was related to the pharmacological activity of TAK-390 as a proton pump inhibitor.

The applicable qualification threshold for the impurity \( \text{(b)(4)} \) would allow for a maximum daily intake of \( \text{(b)(4)} \) mcg, as recommended by ICH Q3B(R2), or approximately \( \text{(b)(4)} \) mg/kg/day if a 60-kg body weight is assumed. The maximum potential daily dose of impurity \( \text{(b)(4)} \) at the proposed limit of \( \text{(b)(4)} \) % is \( \text{(b)(4)} \) mcg (\( \text{(b)(4)} \) mg/kg/day based on an assumed bodyweight of 60 kg), based on the maximum proposed clinical dose of 60 mg (2 x 30 mg) for DEXILANT SoluTab. Since the maximum potential daily intake of \( \text{(b)(4)} \) (\( \text{(b)(4)} \) mcg/day) exceeds the ICH qualification threshold \( \text{(b)(4)} \) mcg/day) at the proposed limit, the sponsor conducted the 4-week oral toxicity study in rats described above to support qualification of \( \text{(b)(4)} \). This study demonstrated that \( \text{(b)(4)} \) was well tolerated at \( \text{(b)(4)} \) mg/kg/day, a dose which is approximately 10 times the maximum potential human dose on a body surface area basis. Therefore, impurity \( \text{(b)(4)} \) is considered to be qualified at \( \text{(b)(4)} \) %.

There are no safety concerns for the excipients contained in Dexilant SoluTab. The maximum potential daily dose of methylacrylate methylmethacrylate methacrylic acid...
copolymers exceeds that of other approved drug products. However, the available nonclinical data provides a reasonable assurance of safety for the higher dose (see section 2.4 for details).

From a nonclinical standpoint, there are no approvability issues. The labeling should be revised as recommended.

12 Appendix/Attachments

N/A

cc: Orig NDA 208,056
dgIEP
DGIEP/PM
DGIEP/D. Joseph
DGIEP/K. Zhang
DGIEP/J. Tomaino

R/D Init.: D. Joseph 10/26/15
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KE ZHANG
12/22/2015

DAVID B JOSEPH
12/22/2015

I concur.