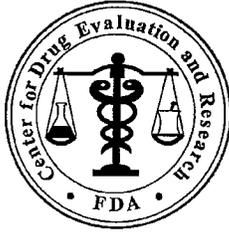


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-287

PROPRIETARY NAME REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

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Subject: Review of Cardiovascular Events and Bone Fracture in the Randomized Clinical Trial of Dexlansoprazole MR Capsules

Drug Name(s): Dexlansoprazole MR Capsules

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EXECUTIVE SUMMARY

Data on cardiovascular adverse events in a clinical trial that randomized subjects to placebo, lansoprazole 30 mg per day, or dexlansoprazole MR 30 mg, 60 mg, or 90 mg per day were reviewed. The data for dexlansoprazole compared with placebo and lansoprazole were not statistically significant for any one specific cardiovascular disorder, although a statistically significant increase was found for dexlansoprazole 30 mg QD compared with lansoprazole 30 mg QD for the category ischemic coronary artery disorders in all phase 3 studies combined. This difference was due to the occurrence of 2 nonfatal myocardial infarctions and 1 angina pectoris (later adjudicated as nonserious angina pectoris) in the dexlansoprazole 30 mg group compared with 0 in the lansoprazole group. Based on data from the U.S. National Hospital Discharge Survey, the rate of nonfatal myocardial infarction in the dexlansoprazole group of 0.21 per 100 person-months is 10 times the expected number of 0.02 per 100 person-months, whereas the rates in the other treatment groups are consistent with the expected number.

No deaths due to cardiovascular disease occurred in any of the treatment arms in any of the studies. No dose-response relationship between dexlansoprazole and cardiovascular outcomes was evident. In addition, all patients who experienced cardiovascular outcomes had pre-existing cardiovascular disorders, cardiovascular comorbidity, and/or cardiovascular risk factors.

Consequently, based on the the absence of cardiovascular fatalities in the Phase 3 studies, the small number of nonfatal cardiovascular outcomes in treatment groups, the lack of statistical significance in the rates of overall and specific cardiovascular outcomes, the absence of a dose-response relationship for dexlansoprazole, the presence of pre-existing cardiovascular disease and/or risk factors in subjects who experienced cardiovascular outcomes, the apparent lack of a plausible biological mechanism of dexlansoprazole, taken short term, in causing or contributing to cardiovascular disorders, and the long-term nature of the atherosclerotic-ischemic process, it does not seem likely that dexlansoprazole is a cause of cardiovascular disorders in the clinical trial data.

Treatment-emergent adverse event data on hip and vertebral fractures and calcium homeostatis indicated that no statistically significant differences existed among the dexlansoprazole, placebo, and lansoprazole groups. No adverse events of hip fracture were reported in the Integrated Summary of Safety or the 4-Month Safety Update data.

1 BACKGROUND

After reviewing the new drug application (NDA 22-287) for dexlansoprazole MR (modified release) (b) (4) Tamara Johnson, M.D., and Keith St. Amand, M.D., Division of Gastrointestinal Products (DGP), expressed concern that there might be an increased risk of cardiovascular disorders with the proton pump inhibitor dexlansoprazole MR based on the randomized clinical trial of various doses of dexlansoprazole MR compared with placebo and lansoprazole. A lesser concern was a possible safety signal for bone fractures with dexlansoprazole MR. They requested that staff of the Division of Epidemiology review the Adverse Events reported in the NDA and other data that had been submitted by the sponsor, TAP Pharmaceutical Products, Inc. "to help evaluate whether there is a safety signal."

2 METHODS

Dr. Johnson provided the following materials for this review:

- 1) the sponsor's Integrated Summary of Safety, Adverse Events subsection;
- 2) the cardiovascular events for lansoprazole, placebo, or active control in the TAP controlled trials database (lansoprazole legacy reports);
- 3) the sponsor's 4-Month Safety Update, Adverse Events subsection;
- 4) the response from TAP to a June 6, 2008 request from DGP for information on dexlansoprazole MR and treatment emergent potential cardiovascular adverse events; and
- 5) Dr. Johnson's slides from an internal FDA presentation on July 24, 2008, and summary table of subjects experiencing a major cardiovascular adverse event in the randomized controlled clinical trial provided on August 1, 2008.

Where possible and relevant, data on cardiovascular outcomes in the clinical trial were compared with U.S. population data for deaths (1) and hospital discharges associated with cardiovascular disease (2) to determine if the clinical trial data observed were consistent with the expected U.S. population data.

3 RESULTS

The various materials reviewed provided somewhat different numbers and information. A review of the data in the Integrated Summary of Safety, the legacy lansoprazole cardiovascular clinical trial data, the 4-Month Safety Update, and the response from TAP to the DGP's information request is provided in sections 3.1-3.4 below. In section 3.5, the data on bone fractures from the Integrated Summary of Safety and the 4-Month Safety Update are reviewed.

3.1 Integrated Summary of Safety Cardiovascular Data

The most salient points and data from the sponsor's Adverse Reactions section of the Integrated Summary of Safety are summarized as follows:

- 1) Concerning the absence of cardiovascular deaths

On pages 137-138, TAP states that among 896 placebo subjects (1.2 average patient-months of exposure), 455 dexlansoprazole MR 30 mg QD (2.1 average patient-months of exposure), 2,311 dexlansoprazole MR 60 mg QD (2.3 average patient-months exposure), 1,864 dexlansoprazole MR 90 mg QD (2.2 average patient-months exposure), and 1,363 lansoprazole 30 mg QD (1.3 average patient-months exposure) in phase 3 studies, 7 subjects died, but there were no cardiovascular deaths (deaths due to heart disease or cerebrovascular disease).

In the United States in 2004, the age-adjusted death rate for all persons for diseases of the heart was 217.0 per 100,000 resident population (1). Converting this rate to person-months, it is $217.0/12 = 18.1$ deaths per 100,000 resident population per month. For males, the age-adjusted death rate for diseases of the heart was 267.9 deaths (or 22.3 per month) and for females it was 177.3 deaths (or 14.8 per month) per 100,000 resident population.

Assuming that the rate of 18.1 deaths per 100,000 population per month is applicable to the clinical trial subjects, we can calculate expected rates and compare them to the observed rates. Of the 12,987.6 person-months of exposure accumulated in the trial (equal to 0.1298 per 100,000 population), we would expect 0.1298×18.1 deaths = 2.3 deaths due to heart disease. By contrast, none was reported.

Similarly, in the United States in 2004, the age-adjusted death rate for all persons for cerebrovascular diseases was 50.0 per 100,000 resident population (1). The rate in person-months would be $50/12 = 4.2$ deaths per 100,000 person months.

Assuming that this rate is applicable to the clinical trial subjects, we can calculate the expected numbers of deaths and compare them to the observed numbers. Of the 12,987.6 person-months of exposure accumulated in the trial (equal to 0.1298 per 100,000 person-months), we would expect 0.1298×4.2 deaths = 0.5 deaths (or 0 to 1 death due to cerebrovascular disease). Consistent with the expected number, no deaths were observed in the trial of this size.

Consequently, assuming that the United States statistics for 2004 apply to the dexlansoprazole clinical trial data, the absence of deaths due to cardiovascular disease in this trial was somewhat lower than the expected number of 2 (for all treatment groups) while the absence of deaths due to cerebrovascular disease was consistent with the expected number.

2) Concerning the nonfatal myocardial infarctions

In Table 44 on pages 142-147, the number of treatment emergent nonfatal serious adverse events and rates per 100 person-months of exposure in all phase 3 studies are provided. There were 2 myocardial infarctions in 955.5 person-months (rate = 0.21 per 100 person months of exposure) with dexlansoprazole MR 30 mg QD and an acute myocardial infarction was reported for dexlansoprazole 60 mg QD (rate = 0.02 per 100 person-months). No nonfatal myocardial infarctions were reported for dexlansoprazole 90 mg, placebo, or lansoprazole. (A coronary artery occlusion was reported for the placebo, but this was later adjudicated as angina).

In the United States in 2004, the rate of discharges from short-stay hospitals for a first-listed diagnosis of acute myocardial infarction (ICD-9-CM code 410) was 25.0 per 10,000 population per year for all ages (or 2.08 per 10,000 person-months = 0.021 per 100 person-months) and 32.5 per 10,000 population per year (or 2.71 per 10,000 person-months = 0.027 per 100 person-months) for those who were 45-64 years old (2). Although based on only two subjects, the rate of nonfatal myocardial infarction of 0.21 per 100 person-months of exposure in the dexlansoprazole 30 mg group is about 10 times higher than expected for the U.S. population while the rate of 0.02 per 100 person-months of exposure in the dexlansoprazole 60 mg group is consistent with the U.S. population rate of 0.021-0.027 per 100 person-months.

All three subjects who developed nonfatal myocardial infarctions had significant cardiovascular medical history and/or risk factors. Subjects 32454009 and 9319002 randomized to dexlansoprazole 30 mg had significant cardiovascular history and risk factors and subject 32849038 randomized to dexlansoprazole 60 mg had cardiovascular risk factors.

3) Increase of ischemic coronary artery category for dexlansoprazole 30 mg

On page 180, the sponsor states that in all phase 3 studies combined, no statistically significant differences between any of the dexlansoprazole MR treatment groups and a comparator group were observed for the *overall* incidence of treatment-emergent potential cardiovascular adverse events. No dose response across the placebo and dexlansoprazole groups was observed for the incidence of any specific potential cardiovascular adverse event.

A statistically significant difference between the dexlansoprazole MR 30 mg treatment group and the lansoprazole 30 mg QD treatment group was observed for the number of subjects per 100 person-months for the category ischemic coronary artery disorders (0.32 versus 0, respectively) (Table 61, page 181). This difference was based on 1 patient with angina pectoris and 2 with myocardial infarction. The incidence of nonfatal myocardial infarction in the dexlansoprazole 30 mg group is about 10 times the U.S. population hospital discharge rate for nonfatal myocardial infarction. The statistically significant difference found for the 30 mg QD dexlansoprazole group versus lansoprazole 30 mg QD was not observed with any of the other dexlansoprazole dose groups. The small numbers of events for dexlansoprazole 30 mg QD, the lack of a dose-response relationship (increasing rates with increasing doses) across the dexlanoprazole treatment groups, and the pre-existing cardiovascular disease in most of the affected patients do not suggest an effect of the drug, taken short-term, as the cause of the cardiovascular events.

5) Concerning the cerebrovascular events

On pages 185-187, the sponsor states that 13 treatment-emergent serious cardiovascular events of interest in 9 subjects occurred in all phase 3 studies. The 9 subjects were randomized to the following treatment groups: 1 subject to placebo, 1 to lansoprazole 30 mg QD, 1 to dexlansoprazole 90 mg QD, 2 to dexlansoprazole 30 mg QD, and and 4 to dexlansoprazole 60 mg QD.

Among the events were coronary artery occlusion (later adjudicated to angina in the placebo group) and myocardial infarctions in 3 subjects (2 in the dexlansoprazole 30 mg dose and 1 in the dexlansoprazole 60 mg dose). Also, there were 3 cerebrovascular events in 3 subjects (a cerebral venous thrombosis and a transient ischemic attack in 2 subjects in the dexansoprazole 60 mg dose, and a cerebrovascular accident in 1 subject in the lansoprazole 30 mg dose group). Apparently the cerebral venous thrombosis (that occurred in a 23-year-old man weighing 291 lbs. with a past history of headaches) and the transient ischemic attack (that occurred after the initial dose of dexlanosoprazole 60 mg in a 51-year-old man with a history of coronary artery disease, hyperlipidemia, diabetes mellitus, hypertension, and unspecified cardiac arrhythmia) were not included in the adjudication process, although the cerebrovascular accident in the lansoprazole group was adjudicated as a nonfatal stroke.

The age-adjusted rate of hospital discharge for cerebrovascular disease in all ages in the United States for 2004 was 31.0 per 10,000 population per year (equal to 2.58 per 10,000 persons per month) (2). Since there were 5,084.2 person-months in the dexlansoprazole 60 mg group, the expected number of hospital discharges for cerebrovascular disease would be 1.31. Since the subject with the transient ischemic attack was hospitalized, the observed number of 2 discharges for cerebrovascular disease in the dexlansoprazole 60

mg group is slightly above but consistent with the expected number (1.31) based on U.S. population data. The expected numbers of cerebrovascular disease for the other groups are: <1 for placebo, <1 for dexlansoprazole 30 mg QD, 1 for the dexlansoprazole 90 mg QD group, and <1 for the lansoprazole group. The numbers observed in the clinical trial are small and consistent with expected numbers.

As shown in Table 62 on pages 187-188, all subjects experiencing treatment-emergent serious cardiovascular events in all phase 3 studies had medical histories, significant cardiovascular comorbidities, and multiple risk factors that would have considerably increased their risk of experiencing serious cardiovascular events.

6) Regarding the Phase 3 long term study

On pages 118-119, 134, and 209-210 of the Integrated Summary of Safety, the Phase 3 long term safety study is discussed. Only treatment-emergent adverse events experienced by $\geq 5\%$ of subjects in any treatment group were provided in Table 39 (page 134). In this table, the number of subjects who took dexlansoprazole was 153 and the number who took the 90 mg dose was 160. No cardiovascular disorders are provided as outcomes in this table.

The 4-Month Safety Update showed that the total number of subjects for dexlansoprazole 60 mg QD remained at 153 while the total number of subjects for dexlansoprazole 90 mg increased to 438 (after the Phase 3 long term safety study data were added). The mean exposure was 225.8 days. No cardiovascular deaths were reported.

3.2 Legacy Lansoprazole Cardiovascular Clinical Trial Data

The most salient points and data from the sponsor's analysis of its legacy lansoprazole clinical trial data concerning adverse cardiovascular events are summarized as follows:

1) Concerning the non-*H. pylori* eradication trials

The randomized clinical trials for non-*H. pylori* eradication trials were 8 weeks in duration; for Phases 2, 3, and 4 randomized clinical trials the mean treatment durations were 1.4 months for each of the three treatment groups. For these trials, 1,627 received placebo, 10,800 received lansoprazole, and 6,868 received an active comparator drug (ranitidine, esomeprazole, omeprazole, or misoprostol). The proportions of subjects who experienced one or more cardiac events of interest in non-*H. pylori* eradication Phase 2, 3, and 4 randomized clinical trials were similar for subjects with ≥ 1 qualified cardiovascular adverse event in any category, and for myocardial infarction, myocardial ischemia, unstable angina, cardiac-related death, and cerebrovascular accident. Two subjects in the placebo group experienced cardiac-related deaths, one in a 43-year-old woman who had a possible pulmonary embolism and the other in a 76-year-old man with a history of cerebrovascular and cardiac disease who received omeprazole and experienced a myocardial infarction associated with a cardiac arrhythmia. There were no clusters of onset or trends in the distribution of events in relation to initiation or duration of treatment for any cardiovascular outcome. Most subjects (89%) with a qualified cardiovascular event had at least one baseline risk factor; 78%, 75%, and 89% had risk factors in the placebo, lansoprazole, and comparator groups, respectively.

2) Concerning the *H. pylori* eradication trials

The randomized clinical trials for *H. pylori* eradication were short in duration--about 7 to 14 days and analysis by time interval was not performed. In these studies, 330 subjects were randomized to receive lansoprazole alone, 1,790 received lansoprazole and antibiotics (clarithromycin or amoxicillin alone, in combination, or in combination with other drugs such as metronidazole, bismuth, and tetracycline), and 253 subjects received antibiotics alone. One subject (0.3%) in the lansoprazole only group, 11 subjects (0.6%) in the lansoprazole and antibiotics group, and 1 subject (0.4%) in the antibiotics only group experienced "myocardial ischemia." It is not clear from the text how myocardial ischemia was defined and diagnosed. Also, there were 2 cerebrovascular accidents (0.1%) in the lansoprazole and antibiotics group. All of the subjects with a qualified cardiovascular event of interest in the *H. pylori* eradication randomized clinical trials had at least one baseline cardiovascular risk factor and the subjects who experienced the cerebrovascular accidents had relevant cardiovascular medical history.

3) Concerning possible mechanisms for cardiovascular effects of lansoprazole

TAP also examined possible mechanisms for cardiovascular effects with the administration of lansoprazole. On page 17, they state that "given its inherently low pH, the canaliculus of the screening gastric parietal cell is the only tissue compartment in the body where the reactive intermediates of lansoprazole should be found at relevant concentrations. Although the same H^+/K^+ -ATPase was found to be present in the heart, the high intracellular pH in the heart (~pH 7.4) would not be expected to allow accumulation or activation of lansoprazole." On page 18, TAP notes that "mild tachycardia (14.4% increase in heart rate) and a slight increase in pulmonary arterial pressure (5.9%) were observed only after the high dose (10 mg/kg) infusion." And in an in vitro efficacy study, lansoprazole bound very weakly to the human histamine-2 (H_2) receptor. The company concluded that "therapeutic concentrations of lansoprazole are highly unlikely to exhibit any activity on the H_2 receptor (with a safety margin of approximately 110-fold based on the free drug C_{max} following the 30 mg dose in humans." They stated that, "None of the studies with lansoprazole had findings that suggested drug-related effects on the heart or blood vessels" and that, "Taken together, the available nonclinical safety studies do not suggest any potential CV effects of lansoprazole."

3.3 Four-Month Safety Update for Dexlansoprazole MR Cardiovascular Clinical Trial Data and Adjudication of Cardiovascular Events

TAP's 4-Month (from Fall 2007, through January 14, 2008) Safety Update provides information from all Phase 3 studies combined which have been updated to include new dexlansoprazole MR 90 mg data from the long-term safety study. There were no new data in the placebo, dexlansoprazole MR 30 mg or 60 mg doses, or the lansoprazole 30 mg dose. The most salient points and data from the sponsor's analysis of cardiovascular events in the 4-Month Safety Update for dexlansoprazole MR capsules, placebo and lansoprazole are as follows:

1) Concerning deaths

On page 53, TAP states that for all phase 3 studies combined (including the Integrated Summary of Safety and the Update), there were no deaths since the ISS. Rates of death (per 100 person-months of exposure) including the updated data were as follows:

placebo, 0; dexlansoprazole 30 mg QD, 0; dexlansoprazole 60 mg QD, 0.09; dexlansoprazole 60 mg QD, 0.02; and lansoprazole 30 mg QD, 0.06. None of the deaths were cardiovascular in nature.

2) Concerning new nonfatal serious adverse events

The new nonfatal serious adverse events from the updated data were listed in Tables 14-16 on pages 55-56, and none were cardiovascular in nature. On page 60, the company stated that for all phase 3 studies combined, "As seen in the ISS, no statistically significant difference between any dexlansoprazole MR treatment group and either the placebo or lansoprazole 30 mg treatment group was observed for the number of subjects per 100 person-months with ≥ 1 nonfatal serious adverse event in the updated analyses or with any specific MedDRA higher level term."

However, we note that in Table 18 (page 61) of the 4-Month Safety Update, the category for ischemic coronary artery disorders for dexlansoprazole 30 mg QD does not list the 1 patient with angina pectoris that was included in this category previously (Table 61, page 181 of the Integrated Summary of Safety). This apparently is due to the adjudication of the angina pectoris as nonserious.

3) On page 76, TAP states that no statistically significant differences between any dexlansoprazole MR treatment group and either the placebo or lansoprazole 30 mg treatment group were observed for the number of subjects per 100 person-months with ≥ 1 treatment-emergent adverse event of interest.

4) In Table 24 of page 79, a statistically significant difference ($p \leq 0.05$) was found for the MedDRA category Ischemic Coronary Artery Disorders between dexlansoprazole 30 mg QD (3 events of 955.5 person-months = 0.32 per 100 person-months) and lansoprazole 30 mg QD (0 events of 1771.9 person-months = 0). The category totals for dexlansoprazole 30 mg QD were based on 2 myocardial infarctions and 1 angina pectoris. In point 2 of section 3.1 above, the occurrence of 2 nonfatal myocardial infarctions in the dexlansoprazole 30 mg QD group is 10 times the expected number based on U.S. hospital discharge data. The angina pectoris case was later adjudicated as nonserious.

5) Concerning a possible error in data

In Table 24 of page 82, for the category Coronary Artery Disorders NEC for the placebo group, 1 event is listed although the table shows that 2 events occurred--1 for coronary artery disease and 1 for coronary artery occlusion. The company should be asked to explain this discrepancy in their numbers.

6) Concerning the adjudication of cardiovascular cases

TAP contracted with a consulting cardiologist,

(b) (4)

(b) (4)

to perform an adjudication

of the cardiovascular events that occurred in the 6,225 subjects of the dexlansoprazole MR Phase 3 studies. The adjudication methods and results were presented on pages 86-94 in the 4-month Safety Update for dexlansoprazole MR capsules, placebo, and lansoprazole. The most salient items and data from this adjudication are summarized as follows:

A total of 281 events in 222 subjects out of 6,225 subjects in the dexlansoprazole MR Phase 3 studies with any signs of symptoms that could be cardiovascular events were sent to (b) (4) for adjudication. The study treatment was blinded. (b) (4) reviewed the spreadsheet of 281 events and identified a subset of subjects that required further evaluation. The number of subjects requiring further evaluation was not stated; however, based on Table 25, it appears that only 16 subjects having 32 cardiovascular events (nonfatal myocardial infarction, angina, possibly cardiac chest pain, and nonfatal stroke) were adjudicated. Unfortunately, the one case of a transient ischemic attack and the one of a cerebral venous thrombosis both in the dexlansoprazole 60 mg group apparently were not adjudicated. The data used for adjudication were the CIOMS reports (for serious events), subject demographics, medical and social histories, adverse events, concomitant medications, and other relevant information.

Of the subjects adjudicated, the adjudication confirmed the following *primary* events experienced by 9 subjects as cardiovascular events: 1 serious angina in placebo; 1 nonserious angina and 2 APTC (Antiplatelet Trialists' Collaboration) nonfatal myocardial infarctions in dexlansoprazole 30 mg QD; 1 nonserious possibly cardiac chest pain, 1 APTC nonfatal myocardial infarction, and 1 serious angina in dexlansoprazole 60 mg QD; 1 nonserious possibly cardiac chest pain in dexlansoprazole 90 mg QD; and 1 APTC nonfatal stroke in lansoprazole 30 mg QD. Four subjects were adjudicated to APTC events; all four had medical history and lifestyle risk factors for cardiovascular disease. The APTC events were serious and occurred within the first 47 days of study drug treatments. Of the 5 subjects assessed as not having APTC events, all but one had an associated medical history or lifestyle risk factor. The subject without significant history underwent cardiac angiography after the event and was found to have atherosclerotic coronary artery and triple vessel disease.

The adjudication found that 5 subjects had nonserious events without enough information available to rule out cardiac origin including 1 with nonserious chest pain and bronchitis in dexlansoprazole 30 mg QD; 2 with nonserious chest pain in dexlansoprazole 60 mg QD; 1 with nonserious shortness of breath in dexlansoprazole 90 mg QD; and 1 with nonserious recurrent supraventricular arrhythmia in lansoprazole 30 mg QD.

TAP stated that the number of subjects with adjudicated cardiovascular adverse events (based on primary diagnoses) per 100 person-months of exposure in the total dexlansoprazole MR group was low (0.06 per 100 person-months) and similar to that of placebo (0.09 per 100 person-months) and lansoprazole groups (0.06 per 100 person-months).

As shown above in the section on the Integrated Summary of Safety, the 2 myocardial infarctions in the 30 mg QD group represent 10 times the expected number of infarctions while the 1 nonfatal myocardial infarction and 2 cerebrovascular events in the dexlansoprazole 60 mg QD group and the nonfatal stroke in the lansoprazole group would be similar to the numbers expected based on U.S. hospital discharge data for acute myocardial infarction and cerebrovascular disease.

3.4 Additional Data from TAP's Response to the June 6, 2008 FDA Information Request and Review of Patient Narratives

On June 6, 2008, staff of the DGP of FDA requested a listing of subjects who experienced at least one potential cardiovascular adverse event in the Phase 3 dexlansoprazole clinical trials and narratives of the adverse event. For this consult, the narratives for the 13 patients with serious cardiovascular events were obtained so that details of patients' histories and illnesses could be reviewed. Narratives revealed that 4 subjects had diagnoses that were not confirmed, 2 had alternative etiologies besides dexlansoprazole that could explain the cardiovascular adverse events, and at least 6 subjects had extensive pre-existing cardiovascular disorders. In addition, the two subjects who experienced nonfatal myocardial infarctions in the dexlansoprazole 30 mg group had discontinued the drug 2 to 4 days before hospitalization for the MIs. Summaries of the 13 subjects with serious adverse events in the dexlansoprazole treatment groups follow:

A 41-year-old woman from the U.S. on dexlansoprazole 60 mg who developed a deep vein thrombosis had been previously hospitalized for treatment of migraine headache with intravenous administration of dihydroergotamine through a peripherally inserted central catheter (PICC line) in her right arm. She developed a cellulitis, deep vein thrombosis, and superficial thrombophlebitis in her right arm. These events were attributed to the PICC line.

The 58-year-old woman from the U.S. who developed a small pulmonary embolism following 12 days of therapy with dexlansoprazole 90 mg was also taking Femhrt, a menopausal hormone, that is a known cause of thromboembolism and pulmonary embolism.

The 65-year-old woman from the U.S. who developed syncope following 99 days of dexlansoprazole 60 mg therapy had syncope 8 months prior to the event onset and prior to taking dexlansoprazole. A Holter monitor performed at the time of the first episode revealed evidence of supraventricular tachycardia and paroxysmal tachycardia. An electrocardiogram performed at the time of the second syncopal episode showed normal sinus rhythm with no ST segment changes. This does not appear to be a true treatment-emergent cardiovascular event.

The 43-year-old woman from the U.S. who developed chest pain (diagnosed as coronary vasospasm) following 31 days of dexlansoprazole 90 mg had an electrocardiogram that showed negative results. Cardiac enzymes were within normal limits. A stress test done at day 33 showed no blockages, and nuclear medicine myocardial diagnostic tests were all within normal limits with a reported ejection fraction of 65%. A cardiologist assessed her chest pain as not likely being due to coronary artery disease. This does not appear to be a true treatment-emergent cardiovascular event.

The 71-year-old woman from the U.S. who was hospitalized due to a myocardial infarction *4 days after discontinuing* dexlansoprazole 30 mg which she had taken for 23 days previously, had a history of diabetes, hypertension, hyperlipidemia, coronary artery disease, peripheral vascular disease, and prior carotid endarterectomy. Her hospitalization was prolonged due to a stroke on about day 30. Coronary angiography revealed multi-vessel disease with left main coronary stenosis and a 4-vessel coronary bypass graft was performed. It seems unlikely that dexlansoprazole taken for 23 days

precipitated a myocardial infarction in this subject who had extensive preexisting coronary artery disease.

The 60-year-old man from the U.S. with a history of asthma, hypertension, sleep apnea, and obesity was hospitalized for a myocardial infarction *two days after discontinuing* dexamprazole 30 mg that he had taken for 28 days previously. During hospitalization he developed cardiogenic shock and sepsis. A cardiac catheterization revealed multivessel coronary disease and he underwent aortocoronary bypass surgery. During hospitalization, the patient was diagnosed with diabetes mellitus, hyperlipidemia, and adrenal insufficiency in addition to the diagnoses listed above. It seems unlikely that dexamprazole taken for 28 days and that was discontinued two days prior to the patient's myocardial infarction had an effect on this subject's extensive coronary artery disease that was likely pre-existing before dexamprazole use.

A 67-year-old man from Latvia with a history of alcohol, tobacco, and caffeine use, had taken dexamprazole 60 mg for 26 days when he developed a non ST-elevation myocardial infarction. The patient had a history of hypertension, but had not undergone previous cardiac testing. He was diagnosed with coronary heart disease, chronic heart failure, and obliterating atherosclerosis of magisterial blood vessels of the legs. It seems improbable that dexamprazole taken for 26 days had an effect on this subject's extensive likely preexisting coronary artery disease. The study drug was maintained during the course of this adverse event.

A 45-year-old man from India with a history of atypical chest pain and retrosternal pain had taken dexamprazole 60 mg for 66 days when he experienced angina. He was recommended to have a cardiac consultation and on the same day he was admitted to a "heart care hospital" where he underwent cardiac angiography which revealed coronary artery disease and triple vessel disease. An echocardiogram revealed an ejection fraction of 56% and an electrocardiogram revealed normal sinus rhythm with minimal ST elevation. Cardiac enzymes were not performed. He subsequently underwent a triple coronary bypass graft. This subject's coronary artery disease appeared to be undiagnosed preexisting disease.

A 61-year-old woman from the U.S. with a history of hypertension and hypercholesterolemia, experienced worsening chest pain and was admitted to hospital for a left heart catheterization. She had been taking dexamprazole 90 mg for 265 days. The catheterization revealed a left ventricle ejection fraction of 60-65% and minimal coronary artery disease. Cardiac markers were negative. This does not appear to be a true treatment-emergent cardiovascular event.

A 48-year-old woman from the U.S. with Turner's syndrome, hypertension, fluctuating blood pressure, hyperlipidemia, diabetes mellitus, obesity, anxiety, mitral valve prolapse, and syncope was hospitalized for "severe syncope," dyspnea, weakness, and hypotension after taking dexamprazole 90 mg for 17 days. A cranial CT scan was normal, electrocardiograms were interpreted as normal or with not clinically significant changes, and serial cardiac enzymes were negative. The event did not appear to be a true treatment-emergent cardiovascular disorder.

A 62-year-old man from the United States with a history of GERD, hypertension, hypercholesterolemia, ischemic heart disease complicated by cardiomyopathy and

congestive heart failure, chronic obstructive pulmonary disease, type II diabetes, heart attack in 2000, and cardiac stent placement in 2005, was hospitalized for worsening coronary artery disease *one day after discontinuing* dexlansoprazole 90 mg which he had taken for five days. A cardiac catheterization revealed recurrent disease in the left anterior descending coronary artery and an occluded right coronary artery. A cardiac stent was placed in the left anterior descending artery. Troponin I levels were within normal limits. The use of the drug for only 5 days and the extensive pre-existing cardiovascular disease make a drug effect an unlikely cause of worsening cardiovascular disease in this subject.

A 51-year old man from the U.S. with a history of erosive esophagitis, coronary artery disease, hyperlipidemia, diabetes mellitus, chronic neuropathic pain, unspecified cardiac arrhythmia, shingles, and hypertension was hospitalized for a transient ischemic attack. The subject had used dexlansoprazole for only *one* day. A CT scan and ECG revealed no acute changes. An MRI of the brain showed multiple old white matter infarcts and carotid dopplers were negative. While the subject's symptoms may have been consistent with a TIA, no evidence of changes were seen in any test results. The subject's extensive cardiovascular history and the use of the drug for only one day does not seem consistent with an effect of the drug in precipitating this event.

A 23-year-old obese male from the U.S. with a past history of headaches, was hospitalized for a cortical venous thrombosis. He had been taking dexlansoprazole 60 mg for 179 days. He was treated with Dilantin, a heparin drip, and an unspecified calcium channel blocker, and post discharge with Coumadin, Kepra, Prilosec and analgesics as needed.

3.5 Hip and Vertebral Fractures or Calcium Hemostasis Adverse Events in all Phase 3 Studies Combined from the Integrated Summary of Safety and the 4-Month Safety Update

In Table 23 on page 77 of the 4-month Safety Update, data are provided on hip and vertebral fractures and calcium homeostasis. Treatment-emergent adverse events for this category included 1 (0.09 per 100 person-months) for placebo, 1 (0.11 per 100 person-months) for dexlansoprazole 30 mg QD, 9 (0.17 per 100 person-months) for dexlansoprazole 60 mg QD, 8 (0.13 per 100 person-months) for dexlansoprazole 90 mg QD, and 3 (0.17 per 100 person-months) for lansoprazole 30 mg QD. There were no statistically significant differences among the groups. The Table notes that no adverse events of hip fracture were reported.

On page 104 of the 4-Month Safety Update, TAP states that, "In the updated analysis, no new treatment-emergent bone and calcium hemostasis adverse event was reported, and no events of hip or vertebral fracture were reported in this update or in the ISS."

In the updated analysis, the number of subjects in the total dexlansoprazole MR group with ≥ 1 treatment-emergent bone and calcium homeostasis adverse event per 100 person-months of exposure was 0.15 per 100 person months. No statistically significant difference between any dexlansoprazole (b) group and a comparator group was observed for the frequency of subjects with a bone and calcium homeostasis adverse event.

4 DISCUSSION

TAP has provided the FDA with data concerning its clinical trial of dexlansoprazole MR compared with placebo and lansoprazole in its Integrated Summary of Safety and a 4-Month Safety Update containing additional data for the dexlansoprazole 90 mg QD dose. In addition, TAP provided cardiovascular data for its legacy lansoprazole clinical trials and also information concerning an adjudication of cardiovascular events in its dexlansoprazole MR clinical trial.

The data for dexlansoprazole compared with placebo and lansoprazole were not statistically significant for any one specific cardiovascular adverse event, although a statistically significant increase was found for dexlansoprazole 30 mg QD compared with lansoprazole 30 mg QD for the category ischemic coronary artery disorders in all phase 3 studies combined (using the 4-Month Safety Update data). This increase was driven by 2 nonfatal myocardial infarctions (adjudicated as myocardial infarctions) and 1 angina pectoris (adjudicated as nonserious angina pectoris) that occurred in the dexlansoprazole 30 mg group compared with 0 in the lansoprazole group. Based on data from the U.S. National Hospital Discharge Survey, the rate of nonfatal myocardial infarction in the dexlansoprazole group is 10 times higher than the national data. However, this difference is based on small numbers in the clinical trial data. No deaths due to cardiovascular disease occurred in any of the studies. No dose-response relationship between dexlansoprazole and myocardial infarction and cardiovascular outcomes was evident. In addition, all patients who experienced cardiovascular outcomes had histories of cardiovascular disorders and/or cardiovascular risk factors such as older age, male sex, hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, overweight/obesity, and previous history of cardiovascular disease. Low levels of exercise, increased caffeine intake, and use of certain medications may also increase risk, while use of aspirin and other medications are associated with decreased risk. Because several risk factors for cardiovascular disease are also risk factors for gastroesophageal reflux disease (e.g., cigarette smoking, overweight/obesity, and increased caffeine intake), the expectation is that studies of individuals with gastroesophageal reflux are likely enriched with subjects at increased risk of cardiovascular outcomes.

Consequently, based on the the absence of cardiovascular fatalities in these studies, the small numbers of nonfatal cardiovascular outcomes in the treatment groups, the lack of statistical significance for the specific and serious outcomes of myocardial infarction and stroke, the absence of a dose-response relationship for dexlansoprazole, the presence of cardiovascular medical history and risk factors in persons experiencing cardiovascular outcomes, the apparent lack of a plausible biological mechanism of the dexlansoprazole, taken short term, in causing or contributing to cardiovascular disorders, and the long-term nature of the atherosclerotic/ischemic process, it does not seem likely that dexlansoprazole is the cause of cardiovascular disorders in the clinical trial data.

In addition, treatment-emergent adverse event data on hip and vertebral fractures and calcium homeostatis indicated that no statistically significant differences existed among the dexlansoprazole, placebo, and lansoprazole groups. No adverse events of hip fracture were reported in the Integrated Summary of Safety or the 4-Month Safety Update data.

5 REFERENCES

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2. DeFrances CJ, Podgornik MN. National Hospital Discharge Survey. Advance data from vital and health statistics; no. 371. Hyattsville, MD: National Center for Health Statistics, 2006.

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Diane Wysowski
8/26/2008 01:24:59 PM
DRUG SAFETY OFFICE REVIEWER

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MEDICAL OFFICER



**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: December 12, 2008
To: Donna Griebel, MD
Director, Division of Gastroenterology Products
Thru: Kristina C. Arnwine, PharmD, Acting Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
From: LaToya Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Proprietary Name, Label and Labeling Review
Drug Name(s): Kapidex (Dexlansoprazole Capsules) 30 mg and 60 mg
Application Type/Number: NDA #22-287
Applicant/sponsor: Takeda
OSE RCM #: 2008-1710

***** This document contains proprietary and confidential information that should not be released to the public. *****

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Kapidex, is not vulnerable to name confusion that could lead to medication error. Thus, DMEPA has no objections to the use of the proprietary name, Kapidex. However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. Additionally, if the product is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This re-review for the proposed name, Kapidex, was written in order to rule out any objections to the proposed proprietary name based upon approval of other proprietary or established names from the signature date of the previous Division of Medication Error Prevention and Analysis name review.

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 the alternate name (b) (4) for review and comment. (b) (4)

Subsequently, the Applicant submitted the proprietary name Kapidex, which was found acceptable on September 12, 2008 in OSE Review 2008-751. The labels and labeling for this product were evaluated in OSE Review 2008-1281 dated August 22, 2008.

(b) (4)

1.3 PRODUCT HISTORY

Kapidex (Dexlansoprazole) is a proton pump inhibitor indicated for healing (b) (4) of all grades of erosive esophagitis, 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 erosive esophagitis is 60 mg once daily for up to 8 weeks. The recommended dose for maintenance of healed erosive esophagitis 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 and 60 mg. 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 the Division of Medication Error Prevention and Analysis (DMEPA) conducting a proprietary name risk assessment (see section 2.1) and label, labeling, and/or packaging risk assessment (see section 2.2). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines 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

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Kapidex, and the proprietary and established names of drug products existing in the marketplace and those pending IND, BLA, NDA, and ANDA products currently under review by CDER.

For the proprietary name, Kapidex, DMEPA searched a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.3). The Division of Medication Error Prevention and Analysis normally conducts internal FDA prescription analysis studies and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment. However, since this name was previously evaluated, FDA prescription analysis studies were not conducted upon re-review of the proprietary name Kapidex.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently lead to medication errors in the clinical setting. The Division of Medication Error Prevention and Analysis defines 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.³ DMEPA uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process,

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

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁴

2.1.1 Search Criteria

DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'K' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter^{5,6}

To identify drug names that may look similar to Kapidex, the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (7 letters), upstrokes (two, capital letter 'K' and lower case letter 'd'), downstrokes (one, lowercase letter 'p'), cross-strokes (one, lower case letter 'x'), and dotted letters (one, lower case 'i'). Additionally, several letters in Kapidex may be vulnerable to ambiguity when scripted, including the letter 'K' may appear as capital letters 'X', 'R', 'B' or 'Y' and lower case 'a' may appear as lower case 'e', 'o', 'c', 'u'; lower case 'p' may appear as lower case 'g' or 'y'; lower case 'i' may appear as lower case 'e' or 'l'; lower case 'd' may appear as lower case 'l' or 'cl'; lower case 'e' may appear as 'a', 'i' or 'l'; and lower case 'x' may appear as lower case 'k', 't', 'n' or 'v'. As such, DMEPA also considers these alternate appearances when identifying drug names that may look similar to Kapidex.

When searching to identify potential names that may sound similar to Kapidex, DMEPA searches for names with similar number of syllables (3), stresses (KAP-i-dex, kap-I-dex or kap-i-DEX), and placement of vowel and consonant sounds. In addition, several letters of Kapidex may be subject to interpretation when spoken including the letter 'K' which may be interpreted as the letter 'C', the letter 'i' may be interpreted as the letter 'a' or 'e' and the letters 'dex' which may be interpreted as 'dix' or 'decks'. As such, the staff also considers there alternate pronunciation when identifying drug names that may sound similar to Kapidex. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

DMEPA also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, DMEPA was provided with the following information about the proposed product: the proposed proprietary name (Kapidex) the established name (Dexlansoprazole), proposed indication (treatment of erosive esophagitis and gastroesophageal reflux disease), strength (30 mg and 60 mg), dose (30 mg and 60 mg depending on indication), frequency of administration (once daily), duration (up to 4 weeks or up to 8 weeks), route of administration (orally) and dosage form of the product (delayed-release capsule). Appendix A provides a more detailed listing of the product characteristics DMEPA generally takes into consideration.

Lastly, DMEPA also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than look and sound-alike name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and DMEPA provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

⁴ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

2.1.2 Database and Information Sources

The proposed proprietary name, Kapidex, was provided to DMEPA to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Kapidex using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.3 CDER Expert Panel Discussion

An Expert Panel Discussion was held by DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Kapidex. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of the Division of Medication Error and Prevention Analysis staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of DMEPA were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁵ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Kapidex convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Kapidex to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

convinced that the names possess similarity that would cause confusion at any point in the medication use system, and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking “Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?” The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator’s Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council’s definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then DMEPA will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, all who have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of

medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

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 labels and carton labeling communicate critical information including proprietary and established name, strength, dosage 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 errors⁶ to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses 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.

On November 21, 2008 the Applicant submitted the following labels and labeling for our review (see Appendix : O, P, Q, R, S, and T)

- Hospital Unit Dose Carton Labeling (100 count): 30 mg and 60 mg
- Professional Sample Blister Card (5 count): 30 mg and 60 mg
- Container Label (30 count, 90 count, 1000 count): 30 mg and 60 mg
- Professional Sample Container Label (7 count): 30 mg and 60 mg
- Professional Sample Blister Tray (5 x5 count): 30 mg and 60 mg
- Professional Sample Container Label (30 count): 60 mg

⁶ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- Package Insert (no image): revised by the Agency as of 12/4/2008

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

Searches identified twenty-seven names as having some similarity to the name Kapidex.

Fifteen of the twenty-seven names were thought to look like Kapidex, which include: Repronex, Ciprodex, (b) (4) Actinex, (b) (4) , Regranex, Xopenex, Rapitux, (b) (4) (b) (4) Feridex IV, Cefotan and Klaridex. Eight of the twenty-seven names were thought to look and sound like Kapidex, which include Kapnax, (b) (4) Kantrex, (b) (4) (b) (4) Casodex, Capoten, and Kapidex***. The remaining four names Capex, (b) (4) were thought to sound similar to Kapidex.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (see section 3.1 above), and noted no additional names.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified six additional names thought to look or sound similar to Kapidex and represent a potential source of drug name confusion. Three names were thought to look like Kapidex, which include: Rapilan, (b) (4) and Rapidin. Two names were thought to look and sound similar to Kapidex and include (b) (4) (b) (4). The last name, Caprylex was thought to sound similar to Kapidex.

As such, a total of thirty-three names were analyzed to determine if the drug names could be confused with Kapidex, and if the drug name confusion would likely result in a medication error.

Failure modes and effects analysis was then applied to determine if the proposed name, Kapidex, could potentially be confused with any of the thirty-three names and lead to medication errors. This analysis determined that the name similarity between Kapidex and the identified names was unlikely to result in medication errors for all thirty-three products for reasons described/outlined in Appendices B through N.

3.2 LABEL AND LABELING RISK ASSESSMENT

Upon review of the revised container labels, carton and insert labeling DMEPA identified one area of vulnerability that could lead to medication errors.

3.2.1 Professional Sample Blister Card (5 count)

After detaching the rebate offer from the 5 count blister packaging, pertinent labeling information including storage recommendations, lot number, date of expiration and the statement "Each capsule contains 30 mg of Dexlansoprazole as enteric-coated granules" will also be removed. The same concern was noted for the 60 mg product.

Note: This is proprietary and confidential information and should not be released to the public

3.2.2 Insert Labeling

No comments

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

We evaluated a total of thirty-three names for their potential confusion with Kapidex. Our FMEA found the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise once the product is commercially marketed. However, DMEPA believes that these limitations are sufficiently minimized by the use of an Expert Panel.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, DMEPA recommends that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

4.2 LABEL AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment found that after detaching the rebate offer from the 5 count blister packaging, pertinent labeling information including storage recommendations, lot number, date of expiration and the statement "Each capsule contains 30 mg of Dexlansoprazole as enteric-coated granules" will also be removed. The same concern was also noted for the 60 mg product. Without this information the drug cannot be identified.

5 CONCLUSIONS

The results of the Proprietary Name Risk Assessment found that the proposed proprietary name, Kapidex, is not vulnerable to name confusion that could lead to medication errors. As such, we do not object to the use of the proprietary name, Kapidex, for this product. Additionally DDMAC does not object to the proposed name, Kapidex, from a promotional perspective.

The Label and Labeling Risk Assessment findings indicate that the design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. We believe the risks identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 6.2.2 that aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

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

6.2 COMMENTS TO THE APPLICANT

A Proprietary Name

We have completed our review of the proposed proprietary name, Kapidex, and have concluded that it is acceptable. Kapidex will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following re-review, we will notify you. If any of the proposed characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

B Label and Labeling Risk Assessment

(b) (4)



7 REFERENCES

1. Review of Safety Applications

OSE Review # 2008-751, September 12, 2008 (Kapidex Proprietary Name Review)

2. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

3. Micromedex Integrated Index (<http://weblern/>)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

4. Phonetic and Orthographic Computer Analysis (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for DMEDP, FDA.

5. Drug Facts and Comparisons, online version, St. Louis, MO (<http://weblern/>)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

6. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

7. Division of Medication Errors and Technical Support proprietary name consultation requests

This is a list of proposed and pending names that is generated by DMEDP from the Access database/tracking system.

8. Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologics, discontinued drugs and “Chemical Type 6” approvals.

9. Electronic online version of the FDA Orange Book
(<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

10. WWW location <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

11. Clinical Pharmacology Online (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

12. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

13. Natural Medicines Comprehensive Databases (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

14. Stat!Ref (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

15. USAN Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

16. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

17. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

18. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compare the spelling of the proposed proprietary name with the proprietary and proper name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., ‘T’ may look like ‘F’, lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Applicant’s intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, DMEPA also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: Names identified in the previous DMEPA review as having some similarity to Kapidex and that have not had changes to their product characteristics and the omission of the Kapidex 90 mg strength will not increase confusion

Proprietary Name	Similarity to Kapidex
Kantrex	Look and Sound
(b) (4)	Look and Sound
Actinex	Look
Capex	Sound
Ciprodex	Look
Xopenex	Look
(b) (4)	Look and Sound
Capoten	Look and Sound
(b) (4)	Look
Casodex	Look and Sound

*****Note: This is proprietary and confidential information and should not be released to the public*****

Appendix C: Proprietary names that lack convincing orthographic and/or phonetic similarities

Proprietary Name	Similarity to Kapidex
Feridex IV	Look
Cefotan	Look
(b) (4)	Sound
(b) (4)	Sound

Appendix D: Proprietary names that are internationally registered

Proprietary Name	Similarity to Kapidex	Active Ingredient	Country
Rapilan	Look	Repaglinide	India
Rapitux	Look	Levodropropizine	Italy
Rapidin	Look	Ranitidine	Phillippines
Kapnax	Look and Sound	Naproxen	Turkey
Kapodin	Look	Minoxidil	Spain
Klaridex	Look	Clarithromycin	Israel

Appendix E: Not found in commonly used references

Proprietary Name	Similarity to Kapidex
(b) (4)	Look

Appendix F: Not identified as a drug and unlikely to be written on a prescription

Proprietary Name	Similarity to Kapidex
(b) (4)	Look

Appendix G: Non-medical product unlikely to be written on a prescription

Proprietary Name	Similarity to Kapidex	
(b) (4)	Look and Sound	Cleaning detergent

Appendix H: Product marketed under a different proprietary name

Proprietary Name	Similarity to Kapidex	Reason for Discard
(b) (4)	Look and Sound	Approved under the name (b) (4)
(b) (4)	Look	Approved under the name (b) (4)

Appendix I: Products not approved by the Agency

Proprietary Name	Similarity to Kapidex	Status
(b) (4)	Look and Sound	(b) (4)

Appendix J: Product likely the sponsor (Takeda) proposed product

Proprietary Name	Similarity to Kapidex
Kapidex***	Look and Sound

Appendix K: Discontinued product with generics available under another proprietary name more likely to be used on a prescription

Proprietary Name	Similarity to Kapidex	Proprietary name likely to be used
Rapdone	Look	Bontril PDM

Note: This is proprietary and confidential information and should not be released to the public

Appendix L: Products with no numerical overlap in strength or dose or if overlap number of tablets needed to achieve dose would cause suspicion or overdose.

Proprietary Name	Similarity to Kapidex	Strength	Usual Dose
Kapidex (dexlansoprazole) delayed-release capsule		30 mg, 60 mg,	<u>Healing of erosive esophagitis:</u> 60 mg once daily for up to 8 weeks <u>Maintenance of Healed erosive esophagitis:</u> 30 mg (b) (4) once daily <u>Symptomatic GERD:</u> 30 mg once daily for 4 weeks

(b) (4)

Appendix M: Products with no numerical overlap in strength and usual dose

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Kapidex (dexlansoprazole) delayed-release capsule		30 mg, 60 mg	<u>Healing of erosive esophagitis:</u> 60 mg once daily for up to 8 weeks <u>Maintenance of Healed erosive esophagitis:</u> 30 mg (b) (4) once daily <u>Symptomatic GERD:</u> 30 mg once daily for 4 weeks
Regranex (Becaplermin)	Look	Topical Gel: 0.01%	Apply to affected area once daily
Caprylex (Caprylic acid)	Sound	400 mg	One to three tablets three times daily on an empty stomach at least one hour before meals

Note: This is proprietary and confidential information and should not be released to the public

Appendix N: Products with potential numerical overlap or similarity in strength and/or dose but multiple differentiating product characteristics

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Differentiating product characteristics
Kapidex (dexlansoprazole) delayed-release capsule		30 mg, 60 mg	<u>Healing of erosive esophagitis:</u> 60 mg once daily for up to 8 weeks <u>Maintenance of Healed erosive esophagitis:</u> 30 mg (b) g once daily <u>Symptomatic GERD:</u> 30 mg once daily for 4 weeks	
Repronex (Mentropins; FSH,LH) injection	Look	75 International Units/Vial	Assisted reproductive technologies: Initial dose; 225 units subcutaneous or intramuscular daily. (Max dose: 450 units). Not to be given beyond 12 days	Dosage form: Capsule vs. Injection Route of Administration: Oral vs. Intramuscular/Subcutaneous Dose: 30 mg or 60 mg vs. 225 units
Kaopek (Attapulgite) oral suspension	Look and Sound	600 mg/15 mL	1200 mg to 1500 mg orally after each loose bowel movement: up to a maximum of 9000 mg/day.	Dosage form: Capsule vs. Suspension Dose: 30 mg or 60 mg vs. 1200 mg to 1500mg Frequency: once daily vs. as needed after each loose stool

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 Trade Secret / Confidential (b4)

 √ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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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: September 12, 2008

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

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

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

Subject: Proprietary Name Review for Kapidex

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

Application Type/Number: NDA # 22-287

Applicant: TAP Pharmaceutical Products

OSE RCM #: 2008-751

*** Note: This review contains proprietary and confidential information that should not be released to the public.***

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Kapidex, has some similarity to other proprietary names, but the findings of the Failure Modes and Effects Analysis (FMEA) indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) does not object to the use of the proprietary name, Kapidex, for this product at this time.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name and its associated labels and labeling be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Gastroenterology Products, for assessment of the proposed proprietary name, Kapidex, regarding its potential confusion with other proprietary or established drug names in the normal clinical practice settings.

Additionally, the Applicant submitted an independent name analysis conducted by (b) (4) (b) (4) for the name Kapidex, and the analysis was evaluated as part of this review.

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 the alternate name (b) (4) for review and comment. DMEPA objected to the use of the name (b) (4) because of the look-alike and/or sound-alike concern with the names (b) (4) (see OSE Review 2008-345 dated August 4, 2008). The labels and labeling for this product were evaluated in OSE Review 2008-1281 dated August 22, 2008.

1.3 PRODUCT INFORMATION

Kapidex (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 (b) (4) 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 the Division of Medication Error Prevention and Analysis staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines 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

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Kapidex, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, Kapidex, the staff of the Division of Medication Error Prevention and Analysis searches a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). Our Division also conducts internal CDER prescription analysis studies (see 2.1.2), and when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.3). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention and Analysis uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur

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

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

at any point in the medication use process, the Division of Medication Error Prevention and Analysis considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³

2.1.1 Search Criteria

The medication error staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'K' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.⁴⁵ Additionally, particular consideration was also given to drug names beginning with the letter 'C', because phonetically the letters 'C' and 'K' sound identical.

To identify drug names that may look similar to Kapidex, the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (two, capital letter 'K' and lower case 'd'), downstrokes (one, letter 'p'), cross-strokes (one, letter 'x'), and dotted letters (one, letter 'i'). Additionally, several letters in Kapidex may be vulnerable to ambiguity when scripted, including the letter 'K' may appear as 'R', 'X', or 'B'; lower case 'a' may appear as lower case 'c', 'e', 'u' or 'o'; lower case 'p' may appear as lower case 'g' or 'y'; lower case 'i' may appear as lower case 'e' or 'l'; lower case 'd' may appear as lower case 'l' or 'cl'; lower case 'e' may appear as 'a', 'i' or 'l'; and lower case 'x' may appear as lower case 'k', 't' or 'v'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Kapidex.

When searching to identify potential names that may look or sound similar to Kapidex, the medication error staff search for names with similar number of syllables (three), stresses (KAP-i-dex or kap-i-DEX), and the placement of vowel and consonant sounds. In addition, several letters in Kapidex may be subject to interpretation when spoken, including the letter 'K' may be interpreted as 'C', the letter 'i' may be interpreted as 'a' or 'e' and the letters 'dex' may be interpreted as 'dix'. As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Kapidex. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the medication error staff were provided with the following information about the proposed product: the proposed proprietary name (Kapidex), the established name (dexlansoprazole), proposed indication (the treatment of erosive esophagitis and gastroesophageal reflux disease), strength (30 mg, 60 mg **(b) (4)** dose (30 mg, 60 mg or **(b) (4)** depending on indication), frequency of administration (daily), duration (up to 4 weeks or up to 8 weeks) route (orally), and dosage form of the product (delayed-release capsules). Appendix A provides a more detailed listing of the product characteristics the medication error staff general take into consideration.

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

⁴ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁵ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Lastly, the medication error staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Kapidex, was provided to DMEPA to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Kapidex using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the medication error staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the medication error staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Kapidex. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Division of Medication Error Prevention and Analysis staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 FDA Prescription analysis studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Kapidex with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Kapidex in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff.

Figure 1 Kapidex Study (conducted on June 2, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Prescription:</u></p> <p><i>Kapidex 30mg po daily</i></p>	<p>"Kapidex 30 mg po daily"</p>
<p><u>Inpatient Prescription:</u></p> <p><i>Kapidex 30 mg 1 tablet by mouth QD</i></p>	

2.1.3 External Proprietary Name Risk Assessment

For this product, the Applicant submitted an independent risk assessment of the proposed proprietary name conducted by a consulting firm. DMEPA conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the medication error staff's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the medication error prevention staff's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the medication error prevention staff provides a detailed explanation of these differences.

2.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

⁶ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: “Is the name Kapidex convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?” An affirmative answer indicates a failure mode and represents a potential for Kapidex to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the name possesses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking “Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?” The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator’s Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. We identify that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council’s definition.
5. The medication error staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while the Division of Medication Error Prevention and Analysis will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then the Division of Medication Error Prevention and Analysis will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by Food and Drug Administration Regulation or by external healthcare authorities, including The Institute of Medicine, The World Health Organization, The Joint Commission, and The Institute for Safe Medication Practices, which have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, the Division of Medication Error Prevention and Analysis contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, the Division of Medication Error Prevention and Analysis believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If we object to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. The Division of Medication Error Prevention and Analysis is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

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3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

In total, forty-one names were identified as having some similarity to the name Kapidex.

Twenty-three of the forty-one names were thought to look like Kapidex, which include: Raptiva, Ropinirole, Kepivance, Naproxen, Kantrex, (b) (4), Kefurox, Lucidex, Lipidex, Rapidvue, Kapectolin, Raplon, Rapaflo, Natalex, Vaginex, Kaylixir, (b) (4), Rapiflux, Repronex, Buprenex, Regranex, (b) (4) and Kaydol.

Seven of the names (Actinex, Capex, (b) (4) Capitis, Capitrol, Aciphex and Tobradex) were thought to sound like Kapidex.

Eleven names thought to look and sound similar to Kapidex were: Kerledex, Casodex, Rapidex, Peridex, Ciprodex, (b) (4) Capoten, Kopodex, Xopenex, and Keflex.

In addition, a search of the USAN Stem List identified no USAN Stems within the proposed name, Kapidex, as of August 1, 2008.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention and Analysis staff (see section 3.1.1. above), and did not note any additional names thought to have orthographic and/or phonetic similarity to Kapidex.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 FDA Prescription Analysis Study

A total of 30 practitioners responded. The majority of the respondents (n=24) interpreted the name correctly as "Kapidex," with correct interpretation occurring more frequently in the inpatient written studies. The remainder of the respondents (n=6) misinterpreted the drug name. Six of the misinterpretations involved the letter "K" being misinterpreted as the letter "C" and four involved the letter "i" being misinterpreted as the letter "o". The majority of misinterpretations occurred in the verbal prescription study. Additionally, four respondents (n=4) in the verbal prescription study misinterpreted the name as "Capodex" which looks and sounds like the currently marketed drug Casodex. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Proprietary Name Risk Assessment

In the proposed name risk assessment submitted by the Applicant, the (b) (4) identified and evaluated a total of thirty-six drug names thought to have some potential for confusion with the name Kapidex. (b) (4) did not specifically list whether they share look-alike and/or sound-alike characteristics with Kapidex. The names identified by (b) (4) were: Actinex, Apidra, Appearex, Aquadeks, Aridex, Aridex-D, Caduet, Candex, Capex, Capoten, Cardec-S, Casodex, Caferject, Ciprodex, Clindex, CP DEC, Guapetex, Icaps, Kadian, Kaletra, Kantrex, Karigel, Keflex, Keppra, Kerodex, Ketek, Kisitex, Kyodex, Lidex, Maxidex, Pendex, Peridex, Poly-Dex, Povidex, Quinidex and Tidex. These thirty-six names were listed in the Computerized Orthographic and Phonologic Analysis (COPA). Twenty-eight of the thirty-six names were not previously identified in our staff searches, the Expert Panel Discussion or FDA prescription studies.

Note: This is proprietary and confidential information and should not be released to the public

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified one additional name thought to look or sound similar to Kapidex and represent a potential source of drug name confusion. Kappadione was thought to look and sound similar to Kapidex. As such, a total of 70 names were analyzed to determine if the drug names could be confused with Kapidex and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Kapidex, and thus determined to represent some risk for confusion. Failure modes and effects analysis was then applied to determine if the proposed name Kapidex could potentially be confused with any of the 70 names and lead to medication error.

This analysis determined that the name similarity between Kapidex and the identified names was unlikely to result in medication error for all 70 products for the reasons described in Appendices C through J.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Seventy names were evaluated for their potential similarity to the proposed name Kapidex. The FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors in a clinical practice setting. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, the medication error prevention staff believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, and, in this case, the data submitted by the Applicant from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Kapidex, is not vulnerable to name confusion that could lead to medication errors. This finding is consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant. As such, DMEPA does not object to the use of the proprietary name, Kapidex, for this product.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention and Analysis has no objections to the use of the proprietary name Kapidex, for this product. However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. If the approval is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, OSE project manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

The Division of Medication Error Prevention and Analysis has no objections to the use of the proprietary name Kapidex for this product. However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. If the approval is delayed beyond 90 days from the signature date of this review, the proposed name will be re-evaluated.

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6 REFERENCES

1. ***Micromedex Integrated Index*** (<http://weblern/>)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention and Analysis, FDA.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO*** (<http://weblern/>)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***AMF Decision Support System [DSS]***

DSS is a government database used to track individual submissions and assignments in review divisions.

5. ***Division of Medication Error Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and “Chemical Type 6” approvals.

7. ***Electronic online version of the FDA Orange Book***
(<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***WWW location*** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

9. ***Clinical Pharmacology Online*** (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

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7 APPENDICES

Appendix A:

The medication error staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention and Analysis also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The medication error staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. The medication error staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the medication error staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we will consider the Applicant’s intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, we also consider a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

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Appendix B:

CDER Prescription Study Responses

Outpatient Prescription	Voice Prescription	Inpatient Medication Order
Kapidex	Capodex	Kapidex
Kapidex	Cathedex	Kapidex
Kapidex	Campidex	Kapidex
Kapidex	Capodex	Kapidex
Kapidex	Kapidex	Kapidex
Kapidex	Capodex	Kapidex
Kapidex	Capodex	Kapidex
Kapidex		Kapidex
		Kapidex

Appendix C: Medical and Non-medical products identified as similar to Kapidex.

Product	Similarity to Kapidex	
Kyodex	COPA	Name of Reagent; no additional information found
Rapidvue	Look	Name of Pregnancy test
Kaydol	Look	Mineral oil
Rapidex	Look/Sound	Skin care exfoliator

Appendix D: Names lacking convincing look-alike and/or sound-alike similarities with Kapidex

Proprietary Name	Similarity to Kapidex	Proprietary Name	Similarity to Kapidex
Raptiva	Look	(b) (4)	COPA
Ropinirole	Look	(b) (4)	COPA
Naproxen	Look	Caduet	COPA
Lucidex	Look	(b) (4)	COPA
(b) (4)	Look	(b) (4)	COPA
Raplon	Look	(b) (4)	COPA
Rapaflo	Look	(b) (4)	COPA
(b) (4)	Look	(b) (4)	COPA
Vaginex	Look	(b) (4)	COPA
Repronex	Look	(b) (4)	COPA
Buprenex	Look	Kaletra	COPA
Regranex	Look	(b) (4)	COPA
Aciphex	Sound	Ketek	COPA
Tobradex	Sound	(b) (4)	COPA
Peridex	Look/Sound	(b) (4)	COPA
(b) (4)	COPA	Quinidex	COPA
(b) (4)	COPA	(b) (4)	COPA
Keppra	COPA		

Appendix E: Identified foreign product name

Proprietary Name	Similarity to Kapidex	Country
Capitis	Look	Argentina
Kopodex	Look/Sound	Chile

Appendix F: Products not approved by the Agency or withdrawn from Agency prior to approval

Proprietary Name	Similarity to Kapidex	Status
(b) (4)	Look	(b) (4)
(b) (4)	Look/Sound	(b) (4)
(b) (4)	Look/Sound	(b) (4)
(b) (4)	Look/Sound	(b) (4)

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Appendix G: Product marketed under a different proprietary name

Proprietary Name	Similarity to Kapidex	Status
(b) (4)	Look	Approved under the name (b) (4)

Appendix H: Discontinued products with no generic equivalent

Proprietary Name	Similarity to Kapidex	Status	Source
Actinex (Masoprocol)	Look/Sound	Discontinued, no generics available	Drugs@FDA/ Orange book/Redbook 2008
Kerledex (Betaxolol hydrochloride; Chlorthalidone)	Look/Sound	Discontinued, no generics available	Drugs@FDA/ Orange book/Redbook 2008
Kappadione (Menadiol Sodium Diphosphate)	Look/Sound	Discontinued, no generics available	Orange book/Redbook 2008
Capitrol (Chloroxine)	Sound	Discontinued, no generics available	Drugs@FDA/ Orange book/Redbook 2008

*****Note: This is proprietary and confidential information and should not be released to the public*****

Appendix I: Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Kapidex (Dexlansoprazole)		30 mg, 60 mg, 90 mg	<u>Healing of erosive esophagitis:</u> 60 mg (b) (4) once daily for up to 8 weeks <u>Maintenance of Healed erosive esophagitis:</u> 30 mg (b) (4) once daily <u>Symptomatic GERD:</u> 30 mg once daily for 4 weeks
Kantrex (Kanamycin Sulfate)	Look	500 mg/2 mL vial 1000 mg/3 mL vial	Individualized dose based on body weight.
Kefurox (Cefuroxime Sodium) (Discontinued but generics available)	Look	0.004% Ophthalmic drops	750 mg to 3 grams every six to eight hours injected into a muscle or vein for 5 to 14 days.
Ciprodex (Ciprofloxacin; Dexamethasone)	Look/Sound	Optic drops: 0.3%; 0.1%	Instill 4 drops in the affected ear twice daily for seven days.
Capoten (Captopril)	Look/Sound	Tablets: 12.5 mg, 25 mg, 50 mg, and 100 mg	Individualized dosing of 25 mg to 150 mg twice a day or three times a day
Keflex (Cephalexin)	Look/Sound	Capsules: 250 mg, 333 mg, 500 mg, and 750 mg	Adult dose ranges from 1 gram to 4 grams daily in divided doses. Usual dose is 250 mg every 6 hours
Apidra (Insulin Glulisine Recombinant)	COPA	100 units/mL vial/cartridge system	Individualized and determined based on the needs of the patient.
Kerodex (OTC)	COPA	Topical; cream	Apply to one-half inch to hands and rub together

Products with no numerical overlap in strength and dose (cont.)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
<p>Kapidex (Dexlansoprazole)</p>		<p>30 mg, 60 mg, 90 mg</p>	<p><u>Healing of erosive esophagitis:</u> 60 mg (b) (4) once daily for up to 8 weeks</p> <p><u>Maintenance of Healed erosive esophagitis:</u> 30 mg (b) (4) once daily</p> <p><u>Symptomatic GERD:</u> 30 mg once daily for 4 weeks</p>
<p>Lidex (Fluocinonide)</p>	<p>COPA</p>	<p>Topical; cream, gel, ointment and solution: 0.05%</p>	<p>Apply to the affected area as a thin film two to four times a day</p>
<p>Regulax SS (Docusate)</p>	<p>Look</p>	<p>Tablets</p>	<p>Take 1 tablet as needed</p>
<p>Lipidex (Nutritional Supplement)</p>	<p>Look</p>	<p>none</p>	<p>Take 6 softgels two times daily with meals</p>
<p>Candex (Nystatin) Discontinued, generics available Candex (Dietary Supplement)</p>	<p>COPA</p>	<p>Topical; Cream and Lotion: 100,000 Units/mL Capsules</p>	<p>Apply to the affected area twice daily Take 2 capsules at least one hour before breakfast and take 2 capsules at bedtime</p>
<p>Kaylixir (Potassium)</p>	<p>Look</p>	<p>Oral solution</p>	<p>Individualized depending on condition 25 to 50 milliequivalents (mEq) dissolved in one-half to one glass of cold water, taken one or two times a day</p>
<p>Capex (Fluocinolone Acetonide)</p>	<p>Sound</p>	<p>Topical; Shampoo: 0.01%</p>	<p>Apply no more than one (1) ounce of shampoo to the scalp area once daily, worked into a lather and allowed to remain on the scalp for approximately 5 minutes. Rinse the hair and scalp completely twice.</p>

Products with no numerical overlap in strength and dose (cont.)

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Kapidex (Dexlansoprazole)		30 mg, 60 mg, 90 mg	<p><u>Healing of erosive esophagitis:</u> 60 mg (b) (4) once daily for up to 8 weeks</p> <p><u>Maintenance of Healed erosive esophagitis:</u> 30 mg (b) (4) once daily</p> <p><u>Symptomatic GERD:</u> 30 mg once daily for 4 weeks</p>
Poly-Dex (Dexamethasone/ Neomycin/Polymyx in B)	COPA	Ophthalmic drops	No additional dosing information found.
Maxidex (Dexamethasone)	COPA	Ophthalmic drops: 0.1% Ophthalmic ointment: 0.05%	<p>Drops: Instill 1 to 2 drops into the conjunctival sac of the affected eye(s) 4 to 6 times daily</p> <p>Ointment: Apply one half to one inch ribbon to the conjunctival sac of the affected eye(s) up to 4 times daily</p>
Aquadeks (Nutritional Supplement)	COPA	Softgels	Take 2 softgels daily

Appendix J: Products with a similar or numerically achievable strength or dose

Failure Mode: Name confusion	Causes (could be multiple)	Effects
<p>Kapidex (Dexlansoprazole) 30 mg, 60 mg, 90 mg delayed release capsules</p>		<p>Usual dose: <i>Healing of erosive esophagitis:</i> 60 mg (b) (4), once daily for up to 8 weeks <i>Maintenance of Healed erosive esophagitis:</i> 30 mg (b) (4) once daily <i>Symptomatic GERD:</i> 30 mg once daily for 4 weeks</p>
<p>Casodex (Bicalutamide) 50 mg tablet (COPA)</p>	<p>Orthographic similarity: Both drugs have similar endings -odex vs. -idex; both share the letter 'a' in the same position</p> <p>Phonetic similarity: Both drugs have three syllables; the beginning sound of the first syllable is the same ('Ca' vs. 'Ka'); the second syllables sound similar 'o' vs. 'i' and the third syllable is identical 'dex'</p> <p>Overlap in route of administration (oral) and frequency of administration (once daily).</p>	<p>Differences in the product characteristics minimize the likelihood of medication errors in the usual practice settings.</p> <p>Rationale: Although the beginnings of both names share the letter 'a' in the same position, the overall beginnings are different (Cas- vs. Kap-). Phonetic differences are provided by the distinct ending sound of the first syllable in each name ('-s-' vs. '-p-').</p> <p>Albeit the products are orthographically and phonetically similar, the differences in product characteristics may help minimize confusion. Casodex is only available in one strength and thus the strength could be omitted, whereas Kapidex is available in multiple strengths and therefore a strength must be specified. Furthermore, Casodex is indicated for the treatment of advanced prostate cancer and therefore would only be prescribed for the specific male patient population. The usual dose is 50 mg once daily to be taken as combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue.</p>
<p>Kepivance (Palifermin) 6.25 mg/vial</p>	<p>Orthographic similarity: Both drugs have similar beginnings Kepi- vs. Kapi</p> <p>Overlap in numerical portion of the usual dose 60 mcg vs. 60 mg</p>	<p>Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting.</p> <p>Rationale: The risk for medication error is minimized by the orthographic differences in the names. The upstroke letter 'd' and the cross stroke letter 'x' in the name Kapidex helps to provide a visual distinction between the names as well as the different endings '-vance' vs. '-dex'. Moreover, the additional 2 letters in Kepivance help to lengthen the name.</p>

		<p>Furthermore, Kepivance is indicated to decrease the incidence and duration of severe oral mucositis and is dosed based on mcg/kg/day. It is also administered as an IV bolus injection for 3 consecutive days and 3 consecutive days after myelotoxic therapy.</p>
<p>Rapiflux (Fluoxetine) (Discontinued product with generic equivalents) 20 mg tablet</p>	<p>Orthographic similarity: Share the same letters – api- near the beginning of the names; both end in the letter “x”; beginning letter “R” can look like the beginning letter “K” when scripted.</p> <p>Numerical overlap in achievable doses. Rapiflux usual dose of 20 mg can attain a dose of Kapidex 60 mg.</p>	<p>Orthographic differences in the names minimize the likelihood of medication errors in the usual practice setting.</p> <p>Rationale: The risk for medication error is minimized by the orthographic differences in the names. The upstroke and downstroke of the letter “f” and the two double upstrokes “f and l” in Rapiflux help to provide distinction.</p> <p>Rapiflux is only available in one strength and thus the strength could be omitted, whereas Kapidex is available in multiple strengths and therefore a strength must be specified. Additionally, if an order for Rapiflux is written for 60 mg, this may alert practitioners as the usual dose is 20 mg.</p>
<p>Xopenex (Levalbuterol Hydrochloride) 0.31 mg, 0.63 mg, and 1.25 mg inhalation solution</p> <p>Xopenex HFA (Levalbuterol Tartrate) 0.045 mg metered inhalation</p>	<p>Orthographic similarity: Share the letters “p”, “e”, and “x” in the same positions; Beginning letter “x” can look like beginning letter “K” when scripted</p> <p>Numerical similarity in strength and dose 0.31 mg vs. 30 mg and 0.63 mg vs. 60 mg</p>	<p>The different product characteristics minimize the likelihood of medication errors in the usual practice setting.</p> <p>Rationale: The risk for medication error is minimized by the product characteristics. Although the names may look similar when scripted an order the differing product characteristics may prevent errors from occurring. Because Xopenex is indicated for the treatment or prevention of bronchospasm in adults and children, the directions of use for the inhalation solution will include “via nebulizer”. Although the beginning numbers of the strengths are similar, the unusual endings ‘1’ and ‘3’ may help to distinguish the products. Furthermore, the recommended starting dose is 0.63 mg three times a day, every 6 to 8 hours, by nebulization for the solution and is 1 to 2 inhalations repeated every 4 to 6 hours for the HFA.</p>

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/s/

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