CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209400Orig1s000

CLINICAL REVIEW(S)
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<td>Division / Office</td>
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<tr>
<td>Reviewer Name(s)</td>
<td>Ryan Raffaelli, MD</td>
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<tr>
<td>Review Completion Date</td>
<td>May 4, 2017</td>
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<tr>
<td>Established Name</td>
<td>Omeprazole delayed release orally disintegrating tablet</td>
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<td>(Proposed) Trade Name</td>
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<td>Dexcel Pharma Technologies Ltd.</td>
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<td>Formulation(s)</td>
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<td>Indication(s)</td>
<td>Treatment of frequent heartburn</td>
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical perspective, this reviewer recommends approval for NDA 209400 (omeprazole delayed release orally disintegrating tablet (ODT), 20 mg) for the claimed indication. The indication is identical to that approved for other marketed formulations of omeprazole at the same dose strength available in the over-the-counter (OTC) setting. This recommendation is based on findings from the bioequivalence and bioavailability studies conducted to support the application, the safety profile of the drug demonstrated in those studies and, in general, by safety data in the extensive postmarketing experience of OTC omeprazole products. Approvability will also depend on the findings from the pharmacokinetics (PK) assessment, the nonclinical review of excipients in the drug product, and the applicant’s acceptance of revised Drug Facts labeling.

1.2 Risk Benefit Assessment

Efficacy
The applicant did not conduct any efficacy studies since this new product is a formulation change for an approved OTC drug, omeprazole, for the identical indication – treatment of frequent heartburn occurring two or more days per week. The dosing is also identical – one tablet (20 mg) daily for 14 days. The regimen may be repeated every four months, but no more than three times per year. The applicant submitted this NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. It relies on the FDA’s previous findings of safety and efficacy for omeprazole approved as NDA 21229 (Prilosec OTC® Delayed Release Tablet, omeprazole magnesium, 20 mg). If data from the bioequivalence and bioavailability assessments are adequate, efficacy may be extrapolated from the approved comparator product (NDA 21229).

Safety
The applicant is proposing a maximum 42-count package size for the product, or 3 courses of treatment (14 daily doses). This is appropriate. If approved, the applicant will be limited to marketing package sizes at the 42-count maximum. We are concerned about overuse and misuse of the product, e.g., use for longer than directed or for conditions that should only be treated under the care of a physician, e.g., ulcer treatment. Consistent with our approach to other PPIs; research has shown that increased package sizing of products leads to increased usage among consumers1,2.

Conversely, limiting pack sizes of medication has been shown to reduce episodes of overconsumption by limiting the immediate availability of the drug to the consumer\(^3\,4\). In order to market larger count package sizes, the applicant will need to provide data demonstrating that consumers can understand the limitations of safe use in the OTC setting, i.e., a maximum of three treatment courses per year.

To support safe use in the OTC market, the applicant provided safety data from its bioavailability trials, postmarketing experience (2008-2016) and published scientific literature. It also proposes a Drug Facts Label (DFL) that includes nearly all important warnings and precautions to support safe and proper use of the product. This reviewer proposes a few additional warnings (see Section 9.2 Labeling Recommendations).

As part of the bioavailability assessment, the applicant conducted two trials. One (Study 150075) was a single center, randomized, single dose, 4-way crossover bioequivalence study in 48 male and female subjects (\(>\) 18 years of age) to compare ODT formulation (20 mg) to delayed release tablet (20 mg) under fasted condition. Standard PK variables were evaluated. Safety assessment included adverse events (AE), vital signs, ECG, oropharyngeal assessments and standard lab evaluations. Bioequivalence standards were consistent with FDA guidance. Both test formulations were well tolerated.

The second trial (Study 150076) was a single center, randomized, single dose, 2-way comparative bioavailability study to assess the food effect on PK of the ODT formulation (20 mg). Eighteen male and female subjects (\(>\) 18 years of age) completed the study. Investigators conducted similar assessments as in Study 150075. Under both conditions, the formulation was well tolerated.

In total, 68 treatment-emergent AEs were reported by 30 subjects who received one dose of the study drug in the above trials. More subjects (N=14) reported AEs (N=24) after taking the test product without water (Study 150075). The most common AE was “headache” (N=11). Five subjects across all treatment groups reported diarrhea. There were no serious AEs or deaths reported and no oropharyngeal irritations based on regularly scheduled oral assessments during the trial durations. No concerning safety issues identified.

Omeprazole was originally approved for Rx marketing status in 1989. It was first approved for OTC status in 2003. Regarding safety in the postmarketing experience, over a period from 2008-2016, the applicant estimates 14-day courses of OTC treatment with omeprazole. The applicant includes the postmarketing safety data


from NDA 22032 (Dexcel’s delayed release omeprazole tablet, 20 mg). It confirms that it does not market an omeprazole ODT formulation in any foreign country.

Databases utilized to support safety of omeprazole in the OTC setting (since 2008):
1) Applicant’s pharmacovigilance database
2) FDA Adverse Event Reporting System (FAERS)
3) National Poison Data System (NPDS)
4) World Health Organization Vigibase (WHO)
5) Drug Abuse Warning Network (DAWN)

Relevant to OTC use of a delayed release omeprazole product, the applicant received 5650 AEs reported by 3466 patients using the delayed release tablet. From FDA Adverse Event Reporting System (FAERS), reports from 3441 patients (16.5%) and 11,198 AEs (9.8%) specifically identified OTC products out of the total number of patients and events with omeprazole (Rx, OTC or unknown) identified as a suspect drug. Common events reported overall included drug ineffective, incorrect dose administration, headache, abdominal pain, constipation, diarrhea and flatulence. Most events were non-serious (94%) and the reports accounted for a small proportion of the approximate  courses over the same timeframe. Data from the applicant’s database and the other postmarketing databases address well known adverse events associated with use of omeprazole and well established drug interactions that are already included on DFLs of OTC PPIs, including omeprazole. See the subsection on “Topics of Safety Interest” in Section 8 Postmarket Experience for details on the more recently described and labeled AEs identified as associated with use of omeprazole and other PPIs. Events also frequently describe use of OTC PPIs for Rx indications, including higher doses and longer treatment periods than the products are approved in the OTC market. With proper OTC use, no new safety signals were identified and the data support the warnings and precautions that the applicant proposes for this new ODT product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable for an OTC product.

1.4 Recommendations for Postmarket Requirements and Commitments

None
2 Introduction and Regulatory Background

2.1 Product Information

Omeprazole is a proton-pump inhibitor (PPI) currently used for the treatment of acid-related gastrointestinal disorders. Like other PPIs, omeprazole is acid-labile and rapidly degraded by gastric acid; therefore, most oral omeprazole formulations available are delivered with enteric coatings as a protection from rapid degradation upon exposure to acid. This gives the formulation its delayed-release characteristic.

Omeprazole was approved as a prescription product in the United States in 1989 and subsequently as an OTC product in June 2003. As a prescription product, it is available in dosage strengths of 10 mg, 20 mg, and 40 mg and is indicated for the short-term treatment of active duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), maintenance treatment of healing of erosive esophagitis (EE), treatment of pathological hypersecretory conditions and H. pylori eradication (when used with clarithromycin and/or amoxicillin). It is also approved in children two years and older for the treatment of GERD.

An OTC omeprazole magnesium delayed release tablet, 20.6 mg (Prilosec OTC®), equivalent to 20 mg omeprazole, is currently marketed for the treatment of frequent heartburn (occurring two or more days a week) in adults 18 years of age and older, used once a day for 14 days. This treatment course maybe repeated every 4 months if necessary, but only for a maximum of three courses in one year. The drug is intended for administration in the morning before eating.

Dexcel Pharma Technologies Ltd. (Dexcel) is seeking approval to market Omeprazole Delayed Release Orally Disintegrating Tablet (omeprazole ODT) 20 mg for OTC use. The proposed dosing and indication for this product is same as the already marketed omeprazole magnesium (Prilosec OTC®) delayed release tablet and Dexcel’s omeprazole delayed release tablet for OTC use (NDA 22032). According to proposed directions for use, once the tablet disintegrates on the tongue, any remaining particles may be swallowed with or without water, and the product should not be broken, crushed or chewed. Alternatively, the product may be swallowed whole, also with or without water.

2.2 Currently Available Treatments for Proposed Indications

There are several approved PPIs marketed for the same indication, treatment of frequent heartburn (occurring two or more days per week), in the OTC setting including:

- Esomeprazole magnesium, 20 mg
- Lansoprazole, 15 mg
- Other omeprazole formulations, 20 mg
There is a PPI combination product, omeprazole and sodium bicarbonate, approved for the same indication where the sodium bicarbonate ingredient aids in absorption of omeprazole. There are OTC products approved for acid-related gastrointestinal disorders (acute relief and prevention of heartburn) such as H₂-receptor antagonists (ranitidine, cimetidine, famotidine, nizatidine) and antacids (aluminum and/or magnesium hydroxide, calcium bicarbonate, sodium bicarbonate).

2.3 Availability of Proposed Active Ingredient in the United States

See Section 2.2. There are several omeprazole formulations available for prescription use at dose strengths 10, 20 and 40 mg.

2.4 Important Safety Issues With Consideration to Related Drugs

Proton pump inhibitors are known to inhibit the activity of some hepatic cytochrome P450 enzymes and, therefore, may decrease the clearance of a variety of drugs including, benzodiazepines, warfarin, phenytoin, and drugs that are metabolized by oxidation in the liver. Class labeling for PPIs has been incorporated in the label regarding potential drug interactions with these drugs. For example, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin may need to be monitored for increases in INR and prothrombin time.

Due to the profound and long lasting inhibition of gastric acid secretion from PPIs, it is theoretically possible that omeprazole may interfere with absorption of a variety of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

The most common adverse effects caused by PPIs are nausea, abdominal pain, constipation, flatulence, and diarrhea. Also reported are subacute myopathy, arthralgias, headaches, and skin rashes. PPIs have a safety track record of more than 26 years of use worldwide, but some new issues have emerged. In 2010, class labeling for prescription use of PPIs was updated to include warnings of increased risk of bone fractures. The epidemiological studies supporting the update identified greatest risk with high dose (> 20 mg omeprazole) or long term use of PPIs (> one year) by users, the majority of whom were > 50 years of age. Thus, FDA determined that fracture risk was low with short term, lower dose OTC use of PPIs. Low serum magnesium levels have also been identified in patients taking PPIs over prolonged periods of time. Symptoms may include muscle spasm, arrhythmia and convulsions. In 2011, FDA determined that use of PPIs according to OTC labeling carried very little risk of
hypomagnesemia and no labeling revisions to Drug Facts have been pursued. In 2012, FDA determined that patients undergoing treatment with PPIs may be at increased risk for Clostridium difficile-associated diarrhea. Because a causal relationship between PPI use and this form of diarrhea could not be excluded, class labeling was approved to warn users to stop use and seek medical advice if they have diarrhea that does not improve while taking PPIs.

These important issues with pharmacologically related products are reflected in the current prescribing information and partly in the OTC label for omeprazole, i.e., the labeled duration and frequency of use factor into the relevance of safety language intended to support safe and proper use in the OTC setting for the approved indication. Also see Section 8 Postmarket Experience.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The marketing of omeprazole was originally approved by the FDA for prescription use under NDA 19-810 (Prilosec®, Aztra-Zeneca) in September 1989 for the treatment of gastric acid-related disorders. As stated above, the drug was approved for OTC marketing status in 2003.

The applicant proposes to rely on FDA’s previous findings of safety and efficacy for the listed drug Prilosec OTC® (omeprazole magnesium delayed release tablet, 20.6 mg (equivalent to omeprazole 20 mg); NDA 21229, AstraZeneca). NDA 21229 was approved with reliance on original data, nonclinical, pharmacodynamics and drug interaction data, supporting approval of NDA 19810 (Prilosec®, omeprazole delayed release capsule, AstraZeneca) for prescription only use. The applicant will also cross-reference data from its own NDA 22032 (omeprazole delayed release tablets, 20 mg).

For this application, the applicant conducted a bioequivalence study to compare the proposed product to the applicant’s omeprazole tablet (NDA 22032) and cross referenced findings from a prior bioequivalence study comparing the applicant’s approved tablet and Prilosec OTC®. A food effect study was also conducted. Dexcel also relies on two clinical trials reported in the scientific literature supporting approval of the safety and efficacy of Prilosec OTC®. Clinical safety of omeprazole is supported by data from the listed drug, clinical trials, published literature and adverse event (AE) reports identified in a variety of postmarketing databases including FDA Adverse Event Reporting System (FAERS), National Poison Data System (NPDS), World Health Organization drug alert and Drug Abuse Warning Network (DAWN) over a time period of collection beginning in 2008.

The details of the applicant’s plan were discussed at a pre-IND meeting (October 6, 2015) and a pre-NDA meeting held on May 9, 2016. In addition to the above plan, agreements between the applicant and FDA addressed the following topics:

- Two pharmacokinetics studies – one bioequivalence and one bioavailability/food effect with adequate data collection to support safety (e.g., oropharyngeal assessments)
  - Applicant proposed and conducted the studies with its approved omeprazole delayed release tablet as the comparator. FDA had recommended using Prilosec OTC® as the comparator since efficacy for OTC use of omeprazole was demonstrated with that product; however, it found the applicant’s proposal acceptable.
  - FDA raised concern about risk for “biocreep,” the potential for higher systemic exposure to omeprazole, within a range of acceptable exposures, which may result in safety issues. Comparing the proposed product with the applicant’s approved product, rather than the original listed drug, could result in a significant exposure difference that could put consumers at risk. FDA advised that the applicant consider this in the design of their studies and noted that the NDA review will address the concern. This will be assessed by reviewers in the Office of Clinical Pharmacology.
  - The NDA needs to include a rationale supporting the safety of using the drug over a 14-day treatment period.

Reviewer’s comment: The applicant provides data supporting the treatment period.

- No other clinical or nonclinical studies required – the ascorbic acid inactive ingredient will be assessed for safety as part of the NDA review
- Submit an overall analysis of postmarketing safety of PPIs for OTC use, including a 120-day safety update post submission
  - Begin the review with the year of initial marketing of NDA 22032 (2007-8).
  - Provide an assessment of AEs reported by pediatric users
  - Provide data tables of Preferred Terms (PT) totaling >1% or >2% of all AEs
  - Assess the following safety topics of interest relevant to all PPIs:
    - Misuse (Rx-only dose strengths in OTC setting; use > 14 days or > 3 14-day courses in one year)
    - Fractures/osteoporosis
    - Clostridium difficile diarrhea
    - Hypomagnesemia symptoms (arrhythmias, muscle spasms, convulsions)
  - Synthesize conclusions from published literature
  - Provide data from ODT formulations marketed in nonprescription settings worldwide
Clinical Review  
Ryan Raffaelli, MD  
NDA 209400  
Omeprazole delayed release orally disintegrating tablet, 20 mg

- Provide data tables with results from the pharmacokinetics studies – no patterns of serious AEs or concerning events (discontinuations) resulted in the studies
- Several considerations were made regarding the manufacture, chemistry and control of the product. These will be addressed by reviewers in Office of Pharmaceutical Quality.

Reviewer’s comment: The applicant addressed all of the above in its application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This electronic submission was of high quality, well organized, and easy to navigate. The 120-day safety update was submitted in January 2017 and included a revised section on data from the National Poison Data System since the original submission referenced only lansoprazole, not omeprazole. There were no clinically relevant requests for information, made of the applicant, that warrant further discussion here.

3.2 Compliance with Good Clinical Practices

The pharmacokinetics (PK) studies conducted to support this application were conducted at [redacted]. Trials were conducted in compliance with 21 CFR 56 and current Good Clinical Practice (cGCP) Guidelines as required by the International Conference on Harmonization, the Declaration of Helsinki (2000), Standard Operating Procedures of the applicant, and the ethical principles of the Directive 2001/20/EC (Europe).

3.3 Financial Disclosures

The applicant submitted FDA Form 3454 with respect to clinical trials (Studies 150075 and 150076) conducted to support this application. It certified that it entered into no financial arrangements with the investigators that may cloud the outcomes of the conducted trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemical name of omeprazole is 5-methoxy-2-[(RS)-[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfanyl]-1H-benzimidazole. The molecular formula is C17H19N3O3S and molecular weight is 345.42. Applicant notes that established shelf-life of drug

Reference ID: 4093614
substance is two years and proposes same for drug product. Applicant seeks categorical exclusion for an environmental assessment.

The to-be-marketed product will be a [redacted] tablet packaged in HDPE bottles with [redacted] caps or in [redacted] blister packs (7-14 tablets/pack; up to 42 count cartons).

Reviewer’s comment: A 42-count carton and 42-count bottle is equivalent to 3 14-day treatment courses, the maximum number allowed as per approved labeling for PPIs used in the OTC setting. This is acceptable and further addressed in Section 1.2 Risk Benefit Assessment.

The tablet will disintegrate when placed on the tongue; i.e., disintegration in no more than (NMT) 30 seconds when placed in mouth. All but two ingredients, [redacted] and strawberry flavor mixture are USP/NF compendial ingredients. The safety of these ingredients should be addressed by Dr. Thompson, the pharmacology/toxicology reviewer.
Table 1: Unit Composition of the Omeprazole delayed release orally disintegrating tablet, 20 mg

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<tr>
<td>Sugar Spheres</td>
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<td>(b)(4)</td>
<td>NF</td>
</tr>
<tr>
<td>Omeprazole</td>
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<td>(b)(4)</td>
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</tr>
<tr>
<td>Sodium Stearate</td>
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</tr>
<tr>
<td>Hypromellose</td>
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<tr>
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<tr>
<td>Talc</td>
<td>(b)(4)</td>
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<tr>
<td>Hypromellose Phthalate</td>
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<tr>
<td>Cetyl Alcohol</td>
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<tr>
<td>Triethyl Citrate</td>
<td>(b)(4)</td>
<td>(b)(4)</td>
<td>USP</td>
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<tr>
<td>Titanium Dioxide</td>
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<tr>
<td>Amino Methacrylate Copolymer</td>
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<td>Colloidal Silicon Dioxide</td>
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<tr>
<td>Ferric oxide</td>
<td>(b)(4)</td>
<td>(b)(4)</td>
<td>USP</td>
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mg=milligrams, NF=National Formulary, USP=United States Pharmacopeia

1Does not remain in the final product

Source: Applicant's submission; Table 1, Quality Overall Summary, Section 2.3.P.1; Module 2.3.P

4.2 Clinical Microbiology

Not applicable
4.3 Preclinical Pharmacology/Toxicology

No new nonclinical studies were conducted as nonclinical support for omeprazole has been previously demonstrated. Dr. Thompson’s review was not yet finalized, but will address the excipients in the drug product. Ascorbic acid (vitamin C) is an excipient added in a higher amount mg) than allowed in the inactive ingredient database for ODT formulations (see applicant’s NDA 208025; lansoprazole; mg ascorbic acid). Also see Sections 7.2.4 Routine Clinical Testing and 8 Postmarket Experience.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

PPIs increase intragastric pH by inactivating secretion of gastric acid from parietal cells in the stomach. Active ingredients, including omeprazole, specifically inhibit (H+/ K+)-ATPase enzyme system (the “proton pump” exchanger) on the surface of the cells, the final step of acid production in the stomach. The effect is on both basal rates and stimulated release of gastric acid.

4.4.2 Pharmacodynamics

No change from approved Rx labeling for omeprazole drug products (e.g., Prilosec®).

4.4.3 Pharmacokinetics

The pharmacokinetics of omeprazole by oral administration have been well characterized. A review of the new findings from the bioavailability studies (150075 and 150076) conducted to support this application has not yet been finalized by the Office of Clinical Pharmacology. In addition to the conducted studies, the applicant also relies on Study AA24171 conducted in 2005 to support approval of NDA 22032 (omeprazole delayed release tablet; Dexcel). That study was to compare the PK of that drug and Prilosec OTC. See relevant reviews in DARRTS for NDA 22032 for details on the study.

Omeprazole is metabolized most extensively by CYP2C19 and CYP3A4 of the hepatic cytochrome P450 system. It can have significant effects on the systemic exposure of a variety of drugs (see Section 9.2 Labeling Recommendations) due to its effect on reducing gastric acidity and its inhibition of CYP2C19. Those interactions are listed in omeprazole labeling and undergo frequent reevaluation.
5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Pharmacokinetics Studies Supporting Omeprazole Delayed Release ODT

<table>
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<tr>
<th>Study ID</th>
<th># Subjects</th>
<th>Description – Treatment Comparison</th>
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<tbody>
<tr>
<td>Study 150075</td>
<td>48</td>
<td>PK profile: omeprazole ODT vs. Dexcel's omeprazole tablet (administered with and without water; after disintegration and swallowed whole) under fasted condition</td>
</tr>
<tr>
<td>Study 150076</td>
<td>18</td>
<td>PK profile: omeprazole ODT bioavailability under fed and fasted condition</td>
</tr>
<tr>
<td>Study AA24171</td>
<td>72</td>
<td>PK profile: Dexcel's omeprazole tablet vs. Prilosec OTC® (submitted and reviewed under NDA 22032)</td>
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</table>

5.2 Review Strategy

This review provides an overall assessment of the proposed new ODT formulation of omeprazole for use in the OTC setting as a treatment for frequent heartburn, an established OTC indication. The review includes assessments of safety data from two new bioequivalence studies and from postmarketing experience of other marketed omeprazole and PPI drug formulations. The applicant submitted a minimally revised postmarketing safety assessment in the 120-day safety update of January 6, 2017. Efficacy has already been demonstrated.

5.3 Discussion of Individual Studies/Clinical Trials

See Office of Clinical Pharmacology review.

6 Review of Efficacy

**Efficacy Summary**

Efficacy of omeprazole has been demonstrated, evidenced by approval of the original NDA. No additional data are necessary to support efficacy for this new proposed formulation as long as the PK assessment can support extrapolation from the approved comparator.

7 Review of Safety

**Safety Summary**

See the subsection on Safety under Section 1.2 Risk Benefit Assessment for the overall summary. Here, this reviewer simply notes that the DFL, with
recommendation for additional proposed warnings (Section 9.2 Labeling Recommendations), includes all important instructions to support safe and proper use of this new formulation of omeprazole. The drug (20 mg dose) has been approved for OTC marketing status since 2003 with a safety profile supporting continued marketing for the proposed indication. Section 7 of this review only includes data collected from two new bioavailability trials in a small population of healthy subjects intended to support extrapolation of safety and efficacy under a 505(b)(2) application, as submitted. Although this new formulation was not formally tested to evaluate its safety under a full treatment course, i.e., daily administration for 14 days, the lack of any sign of oropharyngeal irritation, or concerns about related AEs reported in the bioavailability trials, supports approval as proposed for use in the OTC setting. This reviewer expects that consumers who may suffer oral irritations will quickly determine to stop using the product and either seek another formulation or see their healthcare provider.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study 150075
This was a single center, randomized, single dose, 4-way crossover bioequivalence study in 48 male and female subjects (> 18 years of age) to compare ODT formulation (20 mg) to delayed release tablet (20 mg) under fasted condition. The crossover variable was defined by dose administration – disintegration of tablet without (#1) or with water (#2), swallowed whole with water (#3); or test product – delayed release tablet swallowed with water (#4; reference). Standard PK variables were evaluated. Safety assessment included adverse events (AE), vital signs, ECG, oropharyngeal assessments and standard lab evaluations. Bioequivalence standards were consistent with FDA guidance. Both test formulations were well tolerated.

Study 150076
This was a single center, randomized, single dose, 2-way comparative bioavailability study to assess the food effect on PK of the ODT formulation (20 mg). Eighteen male and female subjects (> 18 years of age) completed the study. Investigators conducted similar assessments as in Study 150075. Under both conditions, the formulation was well tolerated.

Both of the above trials were conducted outside the U.S., but based on the totality of safety data available for omeprazole since original approval, there is no reason to believe that the populations studied would provide findings different from those likely to occur by the U.S. population for whom this product would be indicated.
7.1.2 Categorization of Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA®) version 18.1 used to determine AEs.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not necessary due to small number of reported AEs.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Not applicable in new studies since OTC use is well established. In development of the original prescription product, 3096 subjects were enrolled in clinical trials worldwide for a variety of conditions necessitating treatment with a PPI. In the scientific literature, since 2012, 118641 subjects have been exposed to the drug in clinical trials with doses up to 40 mg and for durations of several years with more than 32 million patient years' exposure to omeprazole.

7.2.2 Explorations for Dose Response

Not applicable for standard 20 mg OTC dose.

7.2.3 Special Animal and/or In Vitro Testing

The applicant conducted an in vitro alcohol dose dumping study that demonstrated premature omeprazole release in the presence of ≥ 40% alcohol by concentration. Omeprazole in the proposed formulation is acid-labile and may be ineffective in the presence of stomach acid, thus, the delayed release formulation. There are no safety concerns with premature drug release in the presence of alcohol. The applicant seeks a waiver for an in vivo alcohol study and proposes to include a warning in the Drug Facts to not take the drug with alcohol (see Section 9.2 Labeling Recommendations). Reviewers from Offices of Clinical Pharmacology and Biopharmaceutics will determine whether a waiver is granted. Also see Sections 4.3 Preclinical Pharmacology/Toxicology and 7.2.4 Routine Clinical Testing relevant to the safety of excipients in the drug product that constitute the orally disintegrating technology.
7.2.4 Routine Clinical Testing

All subjects underwent full oropharyngeal assessments (palatal, sublingual and buccal areas) by physicians or registered nurses intended to evaluate local tolerability of administered doses in the bioavailability studies. Notably, the coating layers around each pellet containing the omeprazole drug substance include an enteric coating so that the omeprazole is unlikely to be exposed to the oral cavity. Any oral irritations would, thus, be the result of exposure to excipients in the drug product.

Assessments were conducted at screening, prior to dosing, 15 minutes after dosing and at the end of each treatment period. The assessments included a severity grade (0-3; normal to ulcerated with vesicles, bullae or other combinations of signs) and inquiry about history of oral discomfort. All observations were documented, including severity of any findings. No findings noted – all subjects had a Grade 0 (normal mucosa) at every assessment. Note that there was a three day washout period between test doses in Study 150075 and a seven day washout between doses in Study 150076. Thus, there was no testing of a period the same as the duration of the proposed treatment length for OTC use, i.e., 14 days.

Reviewer’s comments: The lack of any findings in these, albeit, small (six single, intermittent doses of test product) studies, consistent with other PPI ODTs, supports safe use for the proposed labeled duration of 14 days.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable since these parameters are well characterized.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See Section 2.4 Important Safety Issues With Consideration to Related Drugs.

7.3 Major Safety Results

7.3.1 Deaths

None reported.

7.3.2 Nonfatal Serious Adverse Events

None reported.
7.3.3 Dropouts and/or Discontinuations

One subject discontinued after a single dose in the first test period due to personal reasons.

7.3.4 Significant Adverse Events

None reported.

7.3.5 Submission Specific Primary Safety Concerns

None are noted in the trials that were conducted.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In total, 68 treatment-emergent AEs were reported by 30 subjects who received one dose of the study drug. More subjects (N=14) reported AEs (N=24) after taking the test product without water (Study 150075). The most common AE was “headache” (N=11). Five subjects across all treatment groups reported diarrhea. After taking the product without water, subjects more commonly reported “product taste abnormal” compared to other test conditions. More subjects reported AEs under fed (N=6) than fasting (N=3) condition in Study 150076. One subject reported one AE as moderately severe (nausea), while the remaining AEs were mild. No concerning safety issues identified.

7.4.2 Laboratory Findings

Clinical lab tests were performed including chemistry, hematology and urinalysis with urine and serum pregnancy testing at each change over period and at study exit. Investigators utilized a guide of Biomedical Laboratory Reference and Acceptable Ranges. Abnormal values were repeated and, if clinically meaningful, resulted in a reported AE. All results within normal limits. All pregnancy tests negative.

7.4.3 Vital Signs

Vital signs were part of a screening physical examination conducted for all enrollees. The Investigators established allowable ranges based on internal Standard Operating Procedures. The ranges and measurements were acceptable.

7.4.4 Electrocardiograms (ECGs)

These were performed at screening and study exit and all were normal.
Reviewer’s comments: Listings 16.2.7 and 16.2.8 (Module 5.3.1.2 – Studies 150075 and 150076) providing subject level laboratory, vital sign and ECG data did not identify values that were measured out of range. Since the studies were small and of minimal exposure overall (six total 20 mg doses), this reviewer considers his general overview of the listings acceptable and agrees that no significant findings noted.

7.4.5 Special Safety Studies/Clinical Trials

None conducted.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

Except to comment on drug-drug interactions, no additional evaluations are necessary. See prior safety reviews of approved omeprazole drug products.

7.5.5 Drug-Drug Interactions

None were evaluated in the clinical assessment. Relevant interactions are already identified in labeling and related safety risks are frequently reevaluated.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new nonclinical data were submitted to support safety relevant to risk for carcinogenicity. See existing data used to inform prescription and, thus, nonprescription labeling upon switch of PPIs to OTC marketing status.

7.6.2 Human Reproduction and Pregnancy Data

See section 8.1 of prescription labeling for omeprazole products. The drug carries an FDA Pregnancy Category C since there are no adequate/well-controlled trials with omeprazole in pregnant women. Epidemiologic data have not demonstrated an increased risk of poor pregnancy outcomes or congenital malformations with use during first trimester. However, the drug should only be used during pregnancy if the potential benefits outweigh potential risks to the fetus. Omeprazole is excreted in human milk. Nursing infants may be at risk with exposure to the drug. A similar calculus as that used to decide on taking the drug during pregnancy applies to breastfeeding as well.
7.6.3 Pediatrics and Assessment of Effects on Growth

Dexcel requested a full pediatric waiver from requirements of the Pediatric Research Equity Act (PREA) consistent with all PPIs approved for use in the OTC setting. PPIs are unsafe for use by children in the OTC setting because the underlying cause of heartburn symptoms should be evaluated by a healthcare professional. Thus, PPIs should be used by children only by prescription consistent with section 505B(a)(4)(A)(ii) of the PREA. Following agreement from the FDA Pediatric Review Committee (PeRC), an agreed initial Pediatric Study Plan (iPSP) letter was sent on March 4, 2016.

Safety and effectiveness of omeprazole have been demonstrated in children 1 to 16 years of age for short term treatment of symptomatic gastroesophageal reflux disease (GERD) and erosive esophagitis. According to labeling of Prilosec®, the safety profile appears similar to that of adults.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

As per prescription labeling, doses up to 120 times the recommended dose may result in a variety of symptoms including confusion, drowsiness, rapid heartbeat, nausea and vomiting. Many overdose cases reported in literature describe no apparent effect. There is no known antidote, so treatment is symptomatic and supportive.

A review of National Poison Data System under the American Association of Poison Control Centers identified 406 cases where 120 mg of omeprazole or more was ingested. Of those, 80% reported "no effect" or "not more than minor effect." Of 13 cases noting doses above 1 gram; only three were judged “moderate” (N=2) or “major effect” (N=1). One death was reported – a 96 year old female who took 140 mg omeprazole as part of a multidrug ingestion.

8 Postmarket Experience

See Section 2.4 Important Safety Issues With Consideration to Related Drugs with regard to the extent of the review and safety topics the applicant agreed to address. The applicant notes that the novel omeprazole formulation it proposes is safe for use over the established 14-day dosing interval allowed in the OTC setting for marketed PPIs in the treatment of frequent heartburn in adults.

All excipients except ascorbic acid are present in other ODT forms at the same or lower potencies. Dr. Thompson will address the safety of ascorbic acid, although, it has been recommended for daily intake up to 120 mg. Reports of AEs are frequently made with intake of 10-fold higher amounts. Those events may include gastrointestinal distress (abdominal pain, diarrhea), secondary hyperoxaluria with kidney stone formation, or hemolysis in susceptible individuals. Hyperoxaluria is caused by oxalate formation, a
result of ascorbate metabolism, which may result in stone formation in the presence of urinary calcium. In a safety review of vitamin C intake and exposure, the Institute of Medicine set an upper safe limit of 1800 mg per day for adolescents and adults\(^6\). The quantity of ascorbic acid in the proposed formulation (4 mg) is small and only extreme overuse would be likely to result in any of the above events.

The applicant includes the postmarketing safety data from NDA 22032. It confirms that it does not market an omeprazole ODT formulation in any foreign country.

Databases utilized to support safety of omeprazole in the OTC setting (since 2008):

6) Applicant’s pharmacovigilance database
7) FDA Adverse Event Reporting System (FAERS)
8) National Poison Data System (NPDS)
9) World Health Organization Vigibase (WHO)
10) Drug Abuse Warning Network (DAWN)

Reviewer’s comments: The applicant notes that the FAERS data identify use for mostly prescription only indications. Data from NPDS and DAWN (data collection terminated in 2011) pertain to PPIs as a class. In the 120-day update, the applicant divulged that only lansoprazole data were collected from NPDS. Data on omeprazole were submitted at that time and do not identify any new safety issues.

Applicant’s Database
The applicant conducted a review in April and June 2016 covering a period from 2008-2016 to capture safety data. In total, it found 5660 AEs reported by 3466 patients using the delayed release tablet. Most events were non-serious (94%) and the reports accounted for a small proportion of the approximate distribution over the same timeframe (applicant proposed 14-day courses of treatment). Yearly reports varied in proportion from 7.7% (2014) to 21.1% (2009) of total number of reporters. The most commonly reported System Organ Classes (SOC) were General disorders and administration site conditions (30.7%) and Gastrointestinal disorders (28.9%). Table 3 lists those AEs ≥ 2% of the total identified over the capture period (2008-2016).

Table 3: Adverse Events by System Organ Class (SOC), (≥ 2.0% of Total (N=5650))

<table>
<thead>
<tr>
<th>SOC</th>
<th>Serious AE No. (% SOC total)</th>
<th>Nonserious AE No. (% SOC total)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and Administration site conditions</td>
<td>45 (2.6)</td>
<td>1691 (97.4)</td>
<td>1736 (30.7)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>48 (3.0)</td>
<td>1585 (97)</td>
<td>1633 (28.9)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>47 (9.8)</td>
<td>448 (90.2)</td>
<td>495 (8.8)</td>
</tr>
</tbody>
</table>

Clinical Review
Ryan Raffaeelli, MD
NDA 209400
Omeprazole delayed release orally disintegrating tablet, 20 mg

<table>
<thead>
<tr>
<th>Skin and Subcutaneous tissue disorders</th>
<th>20 (4.9)</th>
<th>379 (95.1)</th>
<th>399 (7.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>21 (8.2)</td>
<td>245 (91.8)</td>
<td>266 (4.7)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective tissue disorders</td>
<td>27 (10.7)</td>
<td>232 (89.3)</td>
<td>259 (4.6)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal disorders</td>
<td>22 (9.8)</td>
<td>209 (90.1)</td>
<td>231 (4.1)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>12 (9.2)</td>
<td>123 (90.8)</td>
<td>135 (2.4)</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>21 (19.6)</td>
<td>92 (80.4)</td>
<td>113 (2.0)</td>
</tr>
</tbody>
</table>

Within the commonly reported SOCs, the most commonly reported Preferred Terms (PT) accounting for more than 2% of the total AEs were drug ineffect (17.2%), diarrhea (5.6%), nausea (3.7%), dizziness (3.2%), drug effect decreased (2.9%), and abdominal pain upper (2.6%).

**FAERS**
As per FDA recommendations, the applicant stratified available data, for omeprazole identified as primary suspect drug, by marketing status, formulation, dose, duration of use, year of reporting, seriousness and age. The search was conducted to include 2008 through March 2016. In total, the applicant captured 114,016 AEs from 20,877 subjects. Of them, 3441 subjects (16.5%) reporting 11,198 AEs (9.8%) specifically identified OTC products. Most of the other AEs can be linked to more serious Rx conditions (e.g., gastric ulcer, helicobacter disease, gastroesophageal reflux disease) requiring the diagnosis and care of a healthcare provider. Where data were provided, 5.9% of subjects (N=1095) reported taking 20 mg per day, the approved OTC dose strength of omeprazole. With regard to dose effects on the quantity of AE reporting, the applicant notes that patients reporting taking 10 mg doses listed 3.3 events on average, whereas subjects taking 60-120 mg reported 5.5 events on average. Where reported, the majority of patients (58.6%) reporting events were 50-79 years of age. There were 57 patients taking OTC omeprazole products who were <18 years of age. They reported 111 AEs. Also where reported, 26.4% of AEs were serious for OTC users versus 71.7% of AEs reported by Rx users or users of unclearly stated marketing status (e.g., identified only the name Prilosec® as the offending drug without noting status). There were 1217 deaths reported for all forms and marketing statuses of omeprazole.

Common events reported overall included headache, abdominal pain, constipation, diarrhea and flatulence. For products identified as OTC, see Table 4. The applicant also listed the number of AEs by NDA number over the same time period. Prilosec OTC (NDA 21229) was implicated in 6621 AEs and a generic delayed release product (ANDA 78878) was implicated in 1393 AEs.
Table 4: OTC Users Reporting Common Adverse Events; >4% of Total (N=3441)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Users reporting AE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug ineffective</td>
<td>367 (10.6)</td>
</tr>
<tr>
<td>Incorrect administration - duration</td>
<td>220 (6.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>241 (7)</td>
</tr>
<tr>
<td>Inappropriate schedule</td>
<td>184 (5.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>186 (5.4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>169 (4.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>167 (4.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>158 (4.6)</td>
</tr>
<tr>
<td>Abdominal pain – upper</td>
<td>136 (4)</td>
</tr>
</tbody>
</table>

Source: Modified from Applicant’s submission, Module 5.3.5.3, Integrated Summary of Safety, Section 9.2, Table 38

Reviewer’s comments: No further details provided on the “Incorrect administration - duration” or “Inappropriate schedule” AEs by Preferred Term (PT). Most likely, consumers use the OTC product for Rx indications at higher doses and for longer treatment periods than the DFL labels allow. To check whether this is the case, this reviewer conducted a quick FAERS search to review the narratives of such reports. Since 2012, a five year period, I found 538 reports associated with “omeprazole,” “omeprazole magnesium,” as single and combination ingredient products, and the two PTs. As expected, a sample of reports describes use for non-OTC indications at higher doses (more than one 20 mg tablet) or for longer than allowed (> 14 days). Some reports simply describe stopping use before completing a treatment course. It is unclear why that decision is considered an AE categorized as “incorrect administration.” The serious cases, a small estimated proportion overall, appeared to be the result of off-label use of OTC omeprazole products for Rx-only indications.

World Health Organization (WHO) VigiBase

The applicant searched the WHO database and safety-related WHO publications covering a period from 2008 to 2016. The publications identified omeprazole as a concomitant drug, but not necessarily all deemed it a suspect drug. No new safety issues were identified and findings were consistent and included with those described in the FAERS subsection above and in the summaries of Topics of Safety Interest below.

Drug Abuse Warning Network (DAWN)

Data from this database is collected only through 2011 and includes all PPIs available in the OTC setting. Since that year, the database has not been maintained and data are being combined into a new program managed by the National Center for Health Statistics. The data on abuse and misuse of PPIs, resulting in emergency department visits, are limited and the applicant notes that there are no safety signals identified.
Data do indicate that emergency visits more frequently occur in PPI users who are 35 years of age and older. Accurate estimates of such visits are only calculable for consumers > 35 years.

Reviewer’s comment: This reviewer finds nothing in the provided data to refute the applicant’s conclusion that there is no safety concern relevant to abuse or misuse. It is likely that most misuse is administration of the OTC PPIs for prescription-only indications. Whether those consumers are under the care of a physician directing their use of an OTC product is unknown, but such misuse cannot be addressed through Drug Facts in any different manner than that in which those labels already inform consumers on proper OTC use.

National Poison Data System

Data was collected from 2008 through November 2016 from 57 poison control centers across the U.S. include unverified public reports of exposure to omeprazole and other PPIs. The data cannot distinguish by marketing status or indication, and few included information on dosing duration, but the majority of those reports described > 3 months' use; much longer than labeled OTC use. In total, 24,763 events reported (approximately 2750 per year), with 284 considered a “major effect” and 22 deaths. Twenty deaths included multidrug exposures. Of the “major effects,” 81.7% were the result of suicide attempts. Fourteen occurred in pregnancies without any moderate or major effects. Adults > 70 years accounted for 13.6% of cases. Over 10,000 pediatric exposures were reported (10229; 41.3% of all cases), but only 839 were associated with the 20 mg OTC dosage form. Children < 10 years of age were reported as exposed to omeprazole in 27% of all cases. Over 95% of the pediatric reports were unintentional exposures or unintentional errors. The applicant comments that, since 2008, child resistant container closures became more widespread for PPI products of both Rx and OTC marketing status, thus possibly reducing poisoning events.

Topics of Safety Interest

See Section 2.4 Important Safety Issues With Consideration to Related Drugs regarding the background support for informing the investigation of certain topics of safety interest.

Reviewer’s comments: This reviewer cannot envision any difference in the proposed ODT formulation that would benefit from additional or alternative investigations into safety topics different from those described here for the applicant’s delayed release tablet. The safety issues have been addressed, where noted, by relevant label warnings approved for marketed PPIs and a complete discussion of the data supporting the issues will not be repeated in this review. Where warnings are not indicated because the association with PPIs does not apply to labeled short term use for OTC
indications, none are listed on Drug Facts. If approved, the proposed product’s labeling will be no different.

**Hypomagnesemia**
In March 2011, FDA communicated this risk with long term use of PPIs or when PPIs are taken with concomitant drugs that may potentiate hypomagnesemia (digoxin or certain diuretics, for example). Five cases of low serum magnesium have been reported in the applicant’s database with its delayed release tablet. Only three reported duration of use (all longer than the Drug Facts allows). Seventy four cases associated with use of OTC omeprazole were identified in FAERS. Where available, reports noted that users had taken the drug for as short as 21 days to as long as five years. Indications for use were all for prescription only (Barrett’s esophagitis, duodenal ulcer, GERD). Minimum duration of use was five months, well beyond the 14 day course approved for use in the OTC setting. While low serum magnesium levels may result in serious effects such as muscle spasms, irregular heartbeat and seizures, these symptoms may not be present as well. Additionally, use of OTC PPIs for longer than labeled does not justify “muddying” the Drug Facts such that consumers may not read or adhere to the warnings that are important for proper OTC use.

**Cardiac symptoms**
Thirty five cases reported and included 22 “palpitations” PTs. Eleven cases (31%) in total were serious. The only serious event reported more than once was the PT “arrhythmia” (N=2). Other sinus arrhythmias, ventricular tachycardia and extrasystoles were reported once each. Ten patients were using the drug for non-OTC indications (gastritis, ulcer, GERD) or non-OTC doses (40 mg/day). Note that the proposed DFL includes contraindications for use with history of lightheadedness, sweating or dizziness with heartburn; or chest/shoulder pain associated with shortness of breath, sweating or spreading pain; or frequent chest pain. A bulleted list is followed by the statement “These symptoms may be signs of a serious condition. See your doctor.”

In a table of cardiac disorders submitted in periodic reports for NDA 22032 (omeprazole delayed release), events were listed with various PTs and outcomes indicated, but lacking any narratives.

**Reviewer’s comments:** Because these AEs were reported under a different NDA, this reviewer did not request narratives since they were likely reviewed at the time of original submission. The table does not provide any information that would impact the proposed label warnings for this product.

Drug Facts for many, but not all OTC PPIs now warn against use if consumers have frequent chest pain or other symptoms that may herald a cardiac cause for “heartburn” symptoms, e.g., lightheadedness or dizziness. Relevant to moving this language from the section of the Drug Facts on precautions, i.e., “Ask a doctor before use if you,” to a contraindication is the clinical review by Dr. Jane Filie for NDA 204655 (esomeprazole...
Clinical Review  
Ryan Raffaelli, MD  
NDA 209400  
Omeprazole delayed release orally disintegrating tablet, 20 mg

magnesium, 20 mg capsule; DARRTS; February 19, 2014) where she reasoned that the “seriousness and urgency to seek medical attention if an ischemic cardiac event is imminent” was not explicit, noting that "signs and symptoms of ischemic cardiac events and GERD overlap." Because PPIs are labeled as providing delayed relief from heartburn symptoms, there was concern that seeking medical attention may also be delayed. The revision was made as part of approval for OTC marketing status of that product. Dr. Theresa Michele, Division Director of DNDP, noted in her review of NDA 204655 (DARRTS; March 28, 2014) that PPIs as a class will be revised to include the above contraindication. See Section 9.2 Labeling Recommendations.

The applicant provided analysis of literature investigating PPI use and cardiovascular outcomes; not heartburn masking cardiovascular disease, but PPIs associated with adverse cardiac events. Where noted, the publications included only long term use of PPIs for Rx indications, thus, applicability to this application for shorter term OTC use is unclear. Other reports did not describe the dose, Rx vs. OTC use, or duration of omeprazole use. In one large systematic review7 of randomized trials and observational studies of PPI use with dual antiplatelet therapy noted that omeprazole did not show a difference in clinical events (unstable angina/non-ST-segment-elevation myocardial infarction).

Fractures and osteoporosis  
In the databases, 10 reports of bone fracture from seven patients using the delayed release omeprazole product. Six cases reported that omeprazole use was “possibly related.” All patients were using the product for longer than labeling allows and for indications only approved for prescription use. In FAERS, 35 bone fractures were reported with use of OTC products. Three of seven reports noted nearly one year of use. Four of nine cases reporting dose noted use of 40 mg per day. In 2010 and 2011, FDA issued safety communications for risk of fracture. Based on review of six epidemiologic studies, FDA concluded that risk was rare if OTC labeling directions were followed for the approved indication. Thus, no label warning was indicated for OTC omeprazole or other PPIs. FDA has also previously argued that Drug Facts labels are more effective when there is less text. Because fracture risk does not appear to be associated with short term PPI use, regardless whether consumers are likely to use the products for Rx-only conditions, Drug Facts should communicate the important warnings for use according to labeling and not include information that may detract from those warnings. There are no new data to support any revisions.

Clostridium difficile diarrhea  
In 2012, FDA issued a safety communication for increased risk of infectious diarrhea when using PPIs. Persons using PPIs are warned to seek medical advice if they

7 Melloni C, JB Washam, S Jones, SA Halim, V Hasselblad, SB Mayer, et. al., 2015, Conflicting Results between Randomized Trials and Observational Studies on the Impact of Proton Pump Inhibitors on Cardiovascular Events when Coadministered with Dual Antiplatelet Therapy, Circ Cardiovasc Qual Outcomes, 8: 47-55.
develop diarrhea that does not improve. While diarrhea is a frequently reported AE with PPI use, no cases of Clostridium infection were reported in the firm’s database.

**Misuse cases**

Misuse cases accounted for 1704 reports. The cases described longer duration of use, higher doses than labeled on Drug Facts, pediatric use (N=54) or off label intervals (more than three courses per year); frequently, the cases identify use for prescription only indications. The most frequently reported cause of “misuse” was > 14 day treatment duration. Serious events accounted for 11%. Misuse-related adverse events categorized by SOCs most frequently came from reports of Gastrointestinal disorders, General disorders and administration site conditions, Nervous system disorders, and Skin and subcutaneous tissue disorders. Regarding pediatric use and AEs, the most commonly reported SOC was Injury, Poisoning and Procedural complications with 10 events, mostly represented by accidental exposures, of which many identified prescription-only indications warranting use. Use of the OTC PPIs for prescription indications is not uncommon.

**Other safety issues**

There have been reports of acute interstitial nephritis (AIN) associated with use of PPIs. In New Zealand, over the capture period, 65 reports have been received by that country’s postmarketing safety monitoring program. Notably, New Zealand has universal health care access and routinely collects health and pharmacy data on its residents. In addition, from 2005 through August 2009, New Zealand investigators followed a national cohort of 572,661 patients with no history of kidney disease who began a new, documented regimen of a PPI (omeprazole, pantoprazole or lansoprazole). Forty six patients met the study definition of a confirmed diagnosis of AIN (hospitalization with an International Classification of Diseases, 9th or 10th revision, (ICD-9 or -10) diagnosis, no alternative etiology, and renal histology, i.e., biopsy. While the PPIs were only available by prescription over the study period, of those definite cases, where reported, 22/35 (63%) took 20 mg omeprazole daily, the OTC dose. Over half of the definite cases (26/46; 56.5%) took another drug or drugs known to be associated with AIN (e.g., NSAIDs, antibiotics, antiepileptics). Another 26 patients were probable cases. Ten controls were selected for each case and age- and sex-matched. Calculated incidence rates (total cases in exposure category (current, recent, or past use) divided by person years of follow up) were 11.98 (95% Confidence Interval, 9.11 – 15.47) and 1.68 (0.91 – 2.86) for current PPI use vs. past use, respectively, per 100,000 person-years. Among patients only dispensed omeprazole, the unadjusted matched odds ratio for definite cases and controls was 4.00 (95% CI 1.70 – 9.42; p = 0.002) for current vs. past use. Current users were those whose PPI supply ended within 30 days of the index, or entry date defining a “case.” Past users’ supply terminated > 90 days before the index date of becoming a “case.” Neither duration of use (≤ 180 days vs. >

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180 days) nor dose response had a significant effect, but risks appeared higher in older users (> 60 years).

In a 2014 review of AIN cases associated with use of PPIs, the Division of Pharmacovigilance II in Office of Surveillance and Epidemiology identified 41 cases that met its definition of a diagnosis of AIN after ≤ eight weeks of use of omeprazole or lansoprazole at OTC dose strength and dosing interval. Median duration of use was 24 days. Of those cases, 37 identified omeprazole as the suspect drug. Most (26/37; 70%) described using the drug for > 14 days. Eleven cases described AIN diagnosis after ≤ 14 days’ use. Twenty seven cases (following use of omeprazole or lansoprazole) reported use for Rx indications (e.g., ulcer prophylaxis, Gastroesophageal Reflux Disease (GERD)). Three reported use for dyspepsia, which could be a description of proper OTC use; 11 did not report an indication. Cases were frequently clouded by co-morbidities, concomitant medications and age where renal toxicity is a risk.

In prescription labeling, omeprazole use is noted as attributed to idiopathic hypersensitivity reactions such as interstitial nephritis. The warning is general noting that AIN can occur at any point during treatment, including within the labeled duration of use for OTC PPIs. The condition results from an inflammatory infiltrate and PPIs are an uncommon cause of idiosyncratic drug-induced disease after variable duration of exposure. While there is a classic triad of symptoms and signs – rash, fever and eosinophilia – associated with AIN, they are not frequently present. More nonspecific symptoms (nausea, malaise), or no symptoms are more likely early in the process. Urinary output or other urinary findings (e.g., hematuria) are not reliable markers either. Thus, it is not clear how effective a warning intended to be specific to the risk for AIN would be to OTC consumers. Notably, a Citizen Petition (Docket No. FDA-2011-P-0741; received October 11, 2011) requested that PPI labels (OTC and prescription) include black box warnings and be prescribed and sold with medication guides, including informing about risk for AIN, in order to strengthen warnings for several conditions. Dr. Theresa Michele, in a brief review, expressed a similar opinion as this reviewer in comments that the AIN risk appears rare, it is idiosyncratic and its symptoms are non-specific, and, therefore, labeling is not warranted. Informed by a review by the Division of Pharmacovigilance II in Office of Surveillance and Epidemiology, this conclusion is reflected in FDA’s October 31, 2014 Citizen Petition response where revisions to only prescription PPI products were made describing risk for AIN. The symptoms of AIN are “indistinguishable from relatively minor viral episodes that would not otherwise require discontinuation” of a PPI. Including a warning would more likely confuse OTC consumers.

Reviewer’s comments: Revising labeling for the entire class of PPIs is an evolving consideration. While this reviewer does not recommend such a revision at this time, FDA may, in the future, consider adding general warnings to OTC PPI labeling to stop
use and seek medical advice for “any new symptoms” or for signs of an allergic reaction to the drug product.

A search of the WHO database identified 48 reports of PPI use associated with cutaneous lupus erythematosus (CLE). A reported odds ratio (ROR) for omeprazole (N=24) was significant at 6.8 (95% CI 4.5 – 10.1). In FAERS, 43 case reports were identified. None of those cases identified an OTC omeprazole product, use of an OTC dose or use over a short term duration. A minimum of three weeks PPI use prior to onset of symptoms was reported in the literature of several cases. While prescription labeling in Europe has been revised to reflect the apparent association, CLE appears to be rare. FDA continues to monitor these cases, but the applicant does not propose any label warning.

In the 2011 Citizen Petition, the requestor stated that PPI use may result in vitamin B12 deficiency due to its dependence on gastric acid for absorption. FDA determined that risk appears increased only with use beyond 14 days. Thus, no warning was warranted for reasons similar to those discussed in the section above on hypomagnesemia and fractures.

With regard to postmarketing safety experience describing drug interactions, the applicant identified 28 reports with its delayed release tablet formulation. Only three were serious and none were unlabeled or raised any new safety concern. The serious reports included the following:

1) 75 year old female taking omeprazole 20 mg and Plavix® 75 mg. Patient reported chest pain and vascular stent occlusion after using omeprazole for six months while on Plavix.
2) 64 year old female taking omeprazole 20 mg and warfarin 5 mg for at least three days. Patient’s INR decreased without any reported clinical consequence.
3) 88 year old male taking omeprazole 20 mg and digoxin for at least 16 days. Patient’s heart rate decreased.

Reviewer’s comments: There was limited detail on the above patients who reported events deemed serious. Because interactions with clopidogrel (Plavix), warfarin and digoxin are labeled, no further investigation necessary; although, known interaction with warfarin results in an increase, not a decrease, in the international normalized ratio (INR). If approved, this product will maintain the complete labeling available with marketed omeprazole and PPI drug products, including all drug interaction warnings and precautions. FDA has considered revising class labeling for OTC PPIs to include a precaution to ask a doctor or pharmacist before use if you are taking “any drug,” since the list of interacting drugs, due to changes in gastric acidity or effects on metabolic enzymes, continues to increase and is likely to increase in the future as new interactions are identified for this class of drugs. See Section 9.2 Labeling Recommendations.
9 Appendices

9.1 Literature Review/References

The applicant searched for relevant safety literature published over a five year duration (2011-2016). It identified 31 studies all describing subjects taking up to 40 mg omeprazole for treatment periods beyond 14 consecutive days. Only one small study\(^9\) evaluated OTC dosing of omeprazole in a small (N=40) randomized trial comparing the drug to Prevacid 24HR\(^\circledR\) (lansoprazole). There were no serious AEs or other events resulting in discontinuation of that study. Most AEs reported were mild in severity and non-specific or labeled, e.g., abdominal pain and headache. A sample of the interesting literature is summarized below:

**Allgood LD\(^10\) (2005)** – In the original trials to evaluate OTC use of omeprazole, subjects with frequent heartburn (two or more days per week) received either one of two treatment doses of omeprazole, 10 mg and 20 mg, or placebo. The trial compared onset of first 24 hour period heartburn free. In total, 3162 randomized adult subjects enrolled in a 14 day treatment period. Overall, the test drugs were well tolerated. Adverse events were similar across dose strengths. Most commonly, diarrhea, headache, respiratory infection and abdominal pain were reported. One subject in the 20 mg arm and four in the 10 mg arm reported serious AEs. The investigators did not consider any to be likely treatment related. There were no deaths.

*Reviewer’s comment: The serious AEs were not identified or further described.*

**Gomm W\(^11\) (2016)** – Investigators sought to determine if elderly (≥ 75 years of age) PPI users without dementia were at higher risk for incident dementia while using PPIs for a long term (at least 18 months). PPI prescriptions and usage by older individuals has increased greatly and the drugs are among the most frequently used (4-fold increase in prescriptions in Germany). A German cohort (N=73679) was followed prospectively with claims and diagnostic data analyzed demonstrating that elderly users had a significant association with dementia (N=29510; hazard ratio 1.38; 95% Confidence Interval 1.04-1.83, p<0.001). Only regular PPI use (a prescription in each of five full quarters in an 18 month interval) identified an at-risk subject. Occasional (< 6 quarters

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of an interval) or no PPI use excluded subjects from analysis. The hazard ratio was lower for occasional PPI use (1.16; 95% CI 1.13 – 1.19). The authors cite literature that PPIs can cross the blood-brain barrier and have affected amyloid cells in mouse studies.

**Reviewer comments:** This is an interesting study with longitudinal data on a well-documented cohort of older patients who may be at risk for dementia with long term use of PPIs. The long term use of PPIs, the missing data on other conditions increasing risk of dementia (e.g., ApoE4 allele carrier), and the lack of information on the reasons for prescribing PPIs limit the applicability of the data to safe OTC use of omeprazole.

**Liang 2015**

Investigators determined to assess the incidence of headache associated with use of PPIs. Headache is a common drug-induced event and may result in poor compliance. In PPI clinical trials, headache is frequently reported. A national health database in Japan was queried for a random sample of subjects with a primary headache diagnosis under a variety of healthcare visits; outpatient, emergency department, etc. Subjects were retrospectively evaluated for use of PPIs (dose and indication not captured) in seven day increments from 7 to 28 days prior to index date of headache. Subjects served as their own control, i.e., non PPI timeframes over the same number of days were used to compare presence or absence of headache. In 279,120 adult patients with a headache diagnosis, the overall adjusted Odds Ratio over a 7 day treatment period was 1.41 aOR; 95% CI 1.14-1.74; p=0.002). Risk was 1.36; 95% CI 1.16-1.59; p<0.001 at 14 days. Risk was higher for lansoprazole and esomeprazole compared to omeprazole (1.04 aOR; 95% CI 0.73-1.49; p=0.824).

**Pouchain 2012**

Investigators compared efficacy of 20 mg omeprazole to an alginate (Gaviscon®; sodium alginate and sodium bicarbonate) for GERD symptoms over a short term treatment period (14 days). In a multicenter, randomized double blind noninferiority trial in otherwise healthy adult subjects with a minimum of two days of heartburn per week, mean onset to symptom free periods were studied. There was no significant difference in symptom free onset among 278 subjects. There were nine discontinuations in the PPI arm. In the omeprazole arm, 14% reported at least one AE with nausea, constipation and rhinopharyngitis the most common (five or fewer subjects). There was one serious event; a subject in the omeprazole arm reported bowel obstruction. The products were generally well tolerated.

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9.2 Labeling Recommendations

This reviewer has no revisions for the proposed language for the Drug Facts submitted by the applicant. There have been recent requests to other NDA holders for additional warnings to OTC PPI labels. The applicant will need to add the following to the Drug Facts for this product and its delayed release tablet for omeprazole (NDA 22032):

- Add “you develop a rash or joint pain” to “Stop use and ask a doctor if” following the bullet that reads “you get diarrhea.”

Reviewer’s comments: There are reports from FAERS, WHO and the published scientific literature of serious cutaneous and systemic lupus erythematosus events associated with use of PPIs. On April 6, 2017, FDA asked the applicant to revise labeling to include the warning for its NDA 22032, omeprazole delayed release tablet, 20 mg.
• Prilosec® Rx labeling now includes a contraindication for use with rilpivirine, an antiretroviral drug. Add a bullet under the “Do not use” section
• Add a warning to “Ask a doctor or pharmacist before use if you are taking” citalopram (depression medicine)

Reviewer’s comment: Antiretroviral drugs containing rilpivirine are specifically distinguished from other antiretroviral drugs in Rx labeling for omeprazole. There appears to be a significant lowering of rilpivirine exposure in the presence of omeprazole (see September 2, 2010 Clinical Pharmacology review for NDA 202022, rilpivirine HCl). This reviewer recommends the same contraindication be included in the DFL and all OTC omeprazole products.

When used concomitantly, omeprazole can effect increased exposure of citalopram increasing risk for QT prolongation (https://www.fda.gov/drugs/drugsafety/ucm297391.htm). This effect is due to citalopram being primarily metabolized by CYP2C19, a cytochrome P450 isoenzyme inhibited by omeprazole. The dose of citalopram must be limited to 20 mg per day. This is best discussed with a healthcare professional.

There are other approved changes to Rx labeling of omeprazole products that may be considered for translation to the DFL and for class labeling for all omeprazole NDAs, and possibly all OTC PPIs. They include, as proposed for the DFL:
• Ask a doctor or pharmacist before use if you are taking St. John’s Wort
• Ask a doctor or pharmacist before use if you are taking rifampin
  o The above drugs induce the enzymes that metabolize omeprazole (CYP2C19 and CYP 3A4) and can decrease that drug’s concentration, possibly resulting in decreased efficacy, but not safety

Also see the subsection entitled “Other Safety Issues” (p. 31) under Section 8 Postmarket Experience for some additional considerations with regard to possible future warnings for class labeling of OTC PPIs.

9.3 Advisory Committee Meeting

Not necessary for this omeprazole product.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RYAN M RAFFAELLI
05/04/2017

FRANCIS E BECKER
05/04/2017

Reference ID: 4093614
## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:** 209400  
**Applicant:** Dexcel Pharma Technologies Limited  
**Stamp Date:** September 6, 2016

**Drug Name:** Omeprazole Delayed Release Orally Disintegrating Tablet, 20 mg  
**NDA/BLA Type:** Standard

On initial overview of the NDA/BLA application for filing:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td><strong>FORMAT/ORGANIZATION/LEGIBILITY</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1. Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).</td>
<td>eCTD</td>
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</tr>
<tr>
<td>2. Is the clinical section legible and organized in a manner to allow substantive review to begin?</td>
<td>X</td>
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<td></td>
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<tr>
<td>3. Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>5. Are all documents submitted in English or are English translations provided when necessary?</td>
<td>X</td>
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<tr>
<td><strong>LABELING</strong></td>
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<tr>
<td>6. Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm</a>)</td>
<td>X</td>
<td></td>
<td></td>
<td>The applicant submitted draft labeling for proposed OTC Drug Facts consistent with approved omeprazole OTC drug products</td>
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<tr>
<td><strong>SUMMARIES</strong></td>
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<tr>
<td>7. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?</td>
<td>X</td>
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<tr>
<td>8. Has the applicant submitted the integrated summary of safety (ISS)?</td>
<td>X</td>
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<tr>
<td>9. Has the applicant submitted the integrated summary of efficacy (ISE)?</td>
<td>X</td>
<td></td>
<td></td>
<td>Clinical summary of efficacy submitted. This is acceptable.</td>
</tr>
<tr>
<td>10. Has the applicant submitted a benefit-risk analysis for the product?</td>
<td>X</td>
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<tr>
<td>11. Indicate if the Application is a 505(b)(1) or a 505(b)(2).</td>
<td>505(b)(2)</td>
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<tr>
<td><strong>505(b)(2) Applications</strong></td>
<td></td>
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<tr>
<td>12. If appropriate, what is the relied upon listed drug(s)?</td>
<td>Prilosec® OTC (omeprazole magnesium; NDA 21229)</td>
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<tr>
<td>13. Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?</td>
<td>X</td>
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<tr>
<td>14. Describe the scientific bridge (e.g., BA/BE studies)</td>
<td>BE study with applicant’s omeprazole tablet (NDA 22032) and cross reference to BE study (omeprazole tablet vs. Prilosec OTC); food effect study</td>
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<tr>
<td><strong>DOSAGE</strong></td>
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File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908
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<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>15. If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>16. Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:</td>
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<td>X</td>
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<tr>
<td>Pivotal Study #2 Indication:</td>
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<tr>
<td>17. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?</td>
<td></td>
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<td>X</td>
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<tr>
<td>18. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</td>
<td></td>
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<td>X</td>
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<tr>
<td>19. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?</td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td><strong>SAFETY</strong></td>
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<tr>
<td>20. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?</td>
<td></td>
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<td>X</td>
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<tr>
<td>21. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?</td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td>22. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?</td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td>23. For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure(^1)) been exposed at the dosage (or dosage range) believed to be efficacious?</td>
<td></td>
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<td>X</td>
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<tr>
<td>24. For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed?</td>
<td></td>
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<td>X</td>
</tr>
</tbody>
</table>

\(^1\) For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 4006617
## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>exposed as requested by the Division?</td>
<td></td>
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<tr>
<td>25. Has the applicant submitted the coding dictionary used for mapping investigator verbatim terms to preferred terms?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>26. Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?</td>
<td>X</td>
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<tr>
<td>27. Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?</td>
<td></td>
<td>X</td>
<td></td>
<td>No adverse dropouts or deaths reported</td>
</tr>
<tr>
<td><strong>OTHER STUDIES</strong></td>
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<tr>
<td>28. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?</td>
<td></td>
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<td></td>
<td>Applicant requests waiver for in vivo alcohol dose dumping study – (+) early release with alcohol, in vitro; label will instruct users not to take with alcohol. See filing review by Office of Clinical Pharm.</td>
</tr>
<tr>
<td>29. For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>PEDIATRIC USE</strong></td>
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<tr>
<td>30. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?</td>
<td>X</td>
<td></td>
<td></td>
<td>Full waiver request (&lt; 18 years of age)</td>
</tr>
<tr>
<td><strong>PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE</strong></td>
<td></td>
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</tr>
<tr>
<td>31. For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see <a href="http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm">http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm</a>)?</td>
<td>X</td>
<td></td>
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<tr>
<td><strong>ABUSE LIABILITY</strong></td>
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<tr>
<td>32. If relevant, has the applicant submitted information to assess the abuse liability of the product?</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td><strong>FOREIGN STUDIES</strong></td>
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<tr>
<td>33. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?</td>
<td>X</td>
<td></td>
<td></td>
<td>Pivotal PK trials conducted in Canada</td>
</tr>
<tr>
<td><strong>DATASETS</strong></td>
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<tr>
<td>34. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?</td>
<td></td>
<td></td>
<td></td>
<td>See filing review by Office of Clinical Pharmacology</td>
</tr>
</tbody>
</table>

2 The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908
### CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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<th>Content Parameter</th>
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<tbody>
<tr>
<td>35. Has the applicant submitted datasets in the format agreed to previously by the Division?</td>
<td></td>
<td></td>
<td></td>
<td>See filing review by Office of Clinical Pharmacology</td>
</tr>
<tr>
<td>36. Are all datasets for pivotal efficacy studies available and complete for all indications requested?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. Are all datasets to support the critical safety analyses available and complete?</td>
<td></td>
<td></td>
<td></td>
<td>See filing review by Office of Clinical Pharmacology</td>
</tr>
<tr>
<td>38. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CASE REPORT FORMS

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>39. Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?</td>
<td>X</td>
<td></td>
<td></td>
<td>All CRFs were submitted</td>
</tr>
<tr>
<td>40. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### FINANCIAL DISCLOSURE

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>41. Has the applicant submitted the required Financial Disclosure information?</td>
<td>X</td>
<td></td>
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</tbody>
</table>

### GOOD CLINICAL PRACTICE

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>42. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? **___Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

There are no fileability issues.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

This reviewer requests that the applicant either provide, or identify the location of its justification for determining that the foreign data, intended to support this application, are applicable to the US population for which the drug is intended.

Ryan Raffaelli, MD  
Reviewing Medical Officer  
Date

Frank Becker, MD  
Clinical Team Leader  
Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RYAN M RAFFAELLI  
10/31/2016

FRANCIS E BECKER  
10/31/2016

Reference ID: 4006617