CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209400Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 13, 2017
From	Francis E. Becker, M.D., F.A.C.P.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 209400
Applicant	Dexcel Pharma Technologies Ltd.
Date of Submission	September 6, 2016
PDUFA Goal Date	July 6, 2017
Proprietary Name / Established (USAN) names	(proprietary name not determined)/ Omeprazole delayed release orally disintegrating tablet
Dosage forms / Strength	Delayed release orally disintegrating tablet / 20 mg
Proposed Indication(s)	1. Treatment of frequent heartburn.
Recommended:	Approval

1. Introduction

Dexcel Pharma Technologies Ltd (DPT; the Sponsor) submitted a 505(b)(2) New Drug Application (NDA) seeking approval to market over the counter (OTC) Omeprazole Delayed Release (DR) orally disintegrating tablet (ODT) 20 mg for the treatment of frequent heartburn. The Sponsor intends to rely upon the Agency's findings of safety and efficacy for the listed drug (LD), Prilosec OTC (omeprazole; AstraZeneca NDA 021229), in conjunction with information from the public domain, to support approval of this application. DPT has conducted a bioequivalence study (Study 150075) and comparative bioavailability (food effect) study (Study 150076) for this application and also intends to rely on Study AA24171 (Omeprazole DR vs. Prilosec ODT) to provide a scientific "bridge" from the proposed product to the Agency's finding of safety and efficacy for Prilosec OTC.

The proposed dosing and indication for this product is the same as for the already marketed omeprazole magnesium (Prilosec OTC®) delayed release (DR) tablet and DPT's omeprazole delayed release tablet for OTC use (NDA 22032). According to the proposed directions for use, 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.

Omeprazole is a proton-pump inhibitor and was approved as a prescription product in 1989 and as an OTC product in June 20, 2003. As a prescription product, it is available in dosage strengths of 10 mg, 20 mg, and 40 mg and is indicated for: 1) the short-term treatment of active duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD); 2) maintenance treatment of healing of erosive esophagitis (EE); 3) treatment of pathological hypersecretory conditions; and 4) H. pylori eradication (when used with clarithromycin and/or amoxicillin). It is also approved in children two years of age and older for the treatment of GERD.

Reference ID: 4111219

2. Background

The marketing of omeprazole was originally approved by the FDA for prescription use under NDA 19810 (Prilosec®, Astra-Zeneca) in September 1989 for the treatment of gastric acid-related disorders. As stated above, it was approved for OTC marketing status in 2003. The Sponsor 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 Sponsor will also cross-reference data from its own NDA 22032 (omeprazole delayed release tablets, 20 mg).

The Sponsor's development plan was discussed at a pre-IND meeting (October 6, 2015) and a pre-NDA meeting (May 9, 2016). Agreement was reached on the two proposed pharmacokinetic studies (one bioequivalence and one bioavailability/food effect) with inclusion of adequate data collection to support safety (e.g., oropharyngeal assessments). Discussion included the following important issues:

- The Sponsor proposed and conducted the studies with its approved omeprazole delayed release tablet as the comparator. FDA had initially recommended using Prilosec OTC® as the comparator since efficacy for OTC use of omeprazole was demonstrated with that product; however, it found the Sponsor'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. FDA expressed concern that comparing the proposed product with the Sponsor's approved product, rather than the original listed drug, could result in a significant exposure difference that could put consumers at risk. FDA advised the Sponsor to consider this in the design of its studies and noted that the NDA review will address the concern.
- FDA noted that the NDA needs to include a rationale supporting the safety of using the drug over a 14-day treatment period.
- FDA agreed that no other clinical or nonclinical studies would be required and that the ascorbic acid inactive ingredient will be assessed for safety as part of the NDA review.
- The Sponsor was advised to submit an overall analysis of postmarketing safety of PPIs for OTC use, including 120-day post-submission safety update, and beginning with the year of initial NDA marketing of NDA 22032 (2007-2008). The safety analysis is to include an assessment of AEs reported by pediatric users, an assessment of safety topics of interest relevant to all PPIs (Misuse, fractures/osteoporosis, Clostridium difficile diarrhea, and hypomagnesemia symptoms including arrhythmias, muscle spasms, and convulsions), synthesized conclusions from published literature, and data from ODT formulations marketed in nonprescription settings worldwide.

3. CMC/Device

Quality assessment was completed by the Quality Review Team (See **Table 1** below) and is detailed in the Integrated Quality Assessment Review (May 23, 2017).

Table 1: Quality Review Team

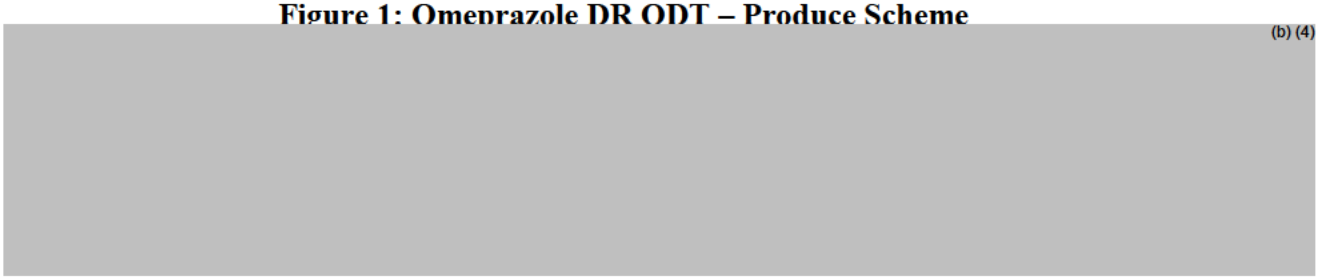
DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Friedrich Burnett, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Krishnaiah Yellela, Ph.D.	OPF/DPAII/BranchVI
Microbiology	Krishnaiah Yellela, Ph.D.	OPF/DPAII/BranchVI
Facility	Carl Lee,	OPF/DIA/B3
Biopharmaceutics	Lee Hansong, Ph.D.	ONDP/DB/BBII
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

In his review, Dr. Swapan De, Application Technical Lead, concluded that, "regarding Chemistry, Manufacturing and Controls, the application may be approved." In addition, Dr. De wrote, "regarding quality aspects of the application the drug substance, drug product, quality biopharmaceutics, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application. The drug product has been granted a shelf life of 24 months under controlled room temperature storage conditions."

Drug Product

Omeprazole is acid labile and therefore administered only as enteric-coated granules in capsules or as enteric-coated tablets. The new dosage form proposed in this application, Omeprazole DR ODT, is an orally disintegrating tablet (b) (4)

Figure 1: Omeprazole DR ODT – Produce Scheme



(Electronically copied and reproduced from Integrated Quality Assessment Review, Figure 3, page 36)

Manufacturing Facility Inspection Report

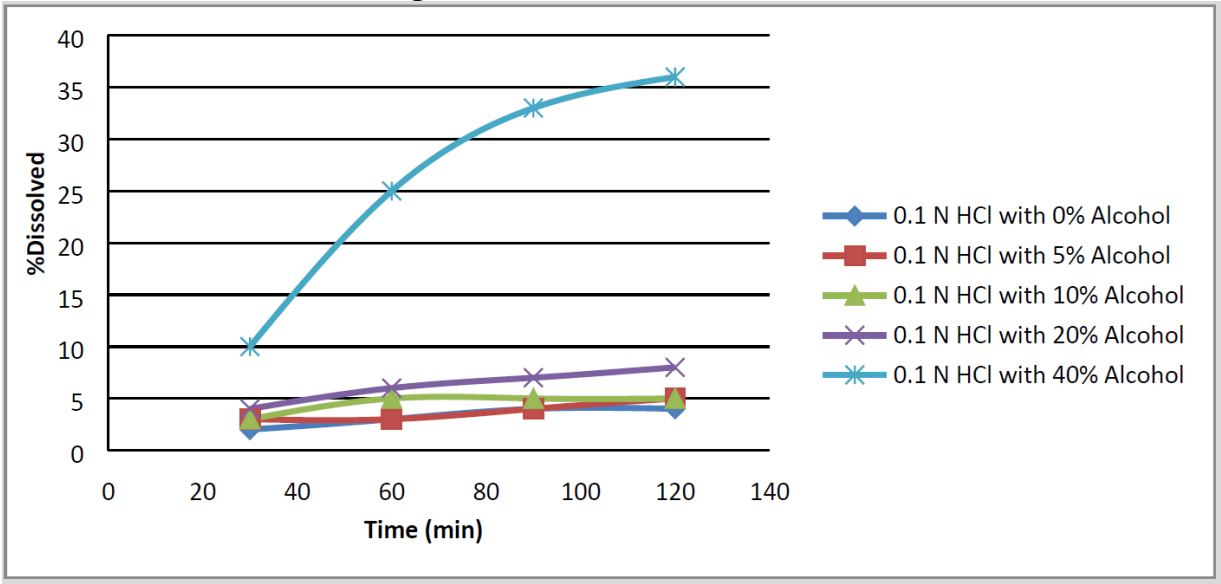
It is noteworthy that the drug substance manufacturing facility ((b) (4)) was initially recommended for "withhold" because of significant GMP deficiencies that were reported on the inspection that ended in (b) (4), and a potential Official Action Indicated (pOAI) alert was entered (Establishment Inspection Report; (b) (4)). The form FDA 483 was issued with four observations, one of which was a deficiency related to omeprazole. (b) (4) The firm ((b) (4) responded to the observations by conducting an investigation which identified (b) (4) The observations and corrective actions were discussed with the Office of Surveillance (OS), Office of Compliance (OC), Drug Shortage Staff (DSS), Office of Pharmaceutical Quality (OPQ), and Office of Regulatory Affairs (ORA). In response, (b) (4) indicated that it has (b) (4) The facility reviewer, Carl Lee, noted that the facility had previously been inspected in (b) (4), receiving classification of No Action Indicated (NAI) each time. He concluded, "Based on acceptable compliance history and no adverse quality trend, this facility is considered acceptable for the proposed functions for NDA 209400."

CDTL Comment: I concur with the conclusions of the facility inspector. It is important to note that the manufacturing facility conducted a complete root cause analysis and did not find any other plausible explanations for the contamination. Furthermore, the manufacturer took appropriate corrective action, and there have been no additional contaminations since (b) (4) *Lastly, the facility has generally been considered to be in good standing, having passed inspections in* (b) (4).

Alcohol Dose Dumping

In vitro alcohol-induced dose dumping testing demonstrated that a concentration of 40% alcohol is likely to cause dose dumping of the proposed product, as shown in **Figure 2** below.

Figure 2: Comparative Dissolution Profile of Tablets from Batch BY501014 in 0.1N HCl Containing 0%, 5%, 10%, 20% and 40% Alcohol



(Electronically copied and reproduced from Integrated Quality Assessment Review, Figure 4, page 175)

The Sponsor submitted a biowaver request for in vivo alcohol-induced dose dumping testing. The Sponsor's product is designed to release all at once but delayed, avoiding the acid environment of the stomach and releasing the drug in the small intestine because omeprazole is unstable in acidic medium. In cases of higher alcohol concentrations, the product is compromised, and the in vivo result will be a premature release of drug in the stomach. Since omeprazole is an acid-labile drug, exposure of the drug to this gastric acid will lead to degradation of omeprazole and result in an ineffective drug. Therefore, co-administration with higher concentrations of alcohol will have an impact on the efficacy, but not the safety, of the drug. The Sponsor has proposed labeling to inform consumers that the product should not be taken with alcohol. The Biopharmaceutics Reviewer deferred to the Office of Clinical Pharmacology as to whether or not an in vivo pharmacokinetic (PK) study is needed.[1]

CDTL Comments: The sponsor's rationale for requesting a biowaiver of in vivo alcohol-induced dose dumping testing is reasonable. The acid-labile omeprazole will be degraded upon early release, so there is no safety concern. The only concern is that the dose will not be efficacious. Under Directions, the proposed Drug Facts Label (DFL) states, "do not take this medicine with alcohol." Even if a consumer took the product with a glass of beer or wine,

[1] The Clinical Pharmacology Review (See **Section 5** below) did not specifically address the requested waiver. Therefore, I initiated email correspondence with the Biopharmaceutics reviewer, Hansong Chen, Pharm. D, Ph.D., and the Clinical Pharmacology reviewer, Jie Cheng, Ph.D. In email communication to me on June 2, 2017, Dr. Chen and Dr. Cheng confirmed that they had discussed the in vitro results and reached agreement that the in vitro study was not needed. Dr. Chen also pointed out that, although the in vitro data show 40% of alcohol is likely to cause dose dumping of the proposed product, "the data are not reliable because omeprazole is not stable under acidic conditions. So far, there is no other better method available for this kind of alcohol dose dumping study."

efficacy would likely not be affected. Efficacy would only be hindered with an alcohol concentration of 40%, equivalent to a shot of alcohol. The Sponsor points out that one shot of alcohol in the evening as a single event will have a lesser effect on efficacy since the drug is to be administered in the morning (Directions state "take one tablet before eating in the morning.") and by evening, most of it will be absorbed to the systemic circulation. Even if this is not the case, if someone took a shot of alcohol with this medication every day for 14 days, he or she would likely not achieve relief of heartburn and should in any case see a physician. The proposed DFL advises to Stop use and ask a doctor if "your heartburn continues or worsens" and "you need to take this product for more than 14 days." FDA has granted biowaivers of in vivo alcohol dose-dumping testing under similar circumstances for other PPI formulations (e.g., Lansoprazole Delayed-Release Orally Disintegrating Tablets; NDA 208025).

Quality Review Team Labeling Recommendations

The Quality Review Team has the following labeling recommendations:

1. Storage statement should be changed to "Store at 20°C - 25°C (68°F - 77°F); keep product out of high heat and moisture"
2. A statement like "do not take this product with alcohol" is recommended.
3. Tamper-evident statement like "do not use if blister is damaged" and "sealed bottle for your protection" may be added if clinically relevant.

CDTL Comments: Agreement was reached with the Sponsor regarding recommended labeling. See ***Section 12****.*

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was completed by D. Charles Thompson, RPh, PhD, DABT, DNDP. In his review (NDA 209400 Nonclinical Review; May 8, 2017), Dr. Thompson concluded that the application is "approvable from nonclinical perspective."

No original nonclinical data were included in this application. Dr. Thompson reported that the proposed drug product formulation contains no novel excipients and that all proposed excipients and/or excipient mixture components are present at in-product use levels that are at or below previously approved use levels for ODT and/or solid oral dosage forms according to current FDA IID reporting, with the exception of ascorbic acid.

Ascorbic acid (Vitamin C) is proposed for use at a level ([(b) (4)] mg/tablet) that is slightly higher than is reported for a previously approved ODT dosage form ([(b) (4)] mg/tablet). The Sponsor submitted a literature-based risk assessment in support of the safety of this slight increase in daily ascorbic acid intake, which Dr. Thompson considered to be adequate. Dr. Thompson concluded that the proposed increase does not raise safety concerns and is acceptable. Furthermore, all specifications for drug substance impurities are at or below the ICH Q3A-prescribed qualification threshold of NMT 0.15% and are consistent with those specified in the current USP monograph for omeprazole.

Reference ID: 4111219

5. Clinical Pharmacology/Biopharmaceutics

As discussed above, the Sponsor intends to rely on the approved Prilosec OTC (NDA 21229; omeprazole magnesium delayed-release tablet, approved 20 June 2003) to support efficacy and safety of the proposed product. In order to support the reliance on Prilosec OTC, the Sponsor provided the results of two bioequivalence studies: 1) Study 150075 between the proposed omeprazole ODT and the omeprazole delayed-release tablet for OTC use (NDA 22032; omeprazole DR); and 2) Study AA24171 between omeprazole DR and Prilosec OTC. Omeprazole DR for OTC use was approved on 4 December 2007 based on bioequivalence with Prilosec OTC as demonstrated in Study AA24171. In addition, a food effect study (150076) was conducted. See **Table 2** below.

Table 2: Pharmacokinetic Studies Supporting Omeprazole Delayed-Release ODT

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

(Electronically copied and reproduced from Dr. Raffaelli's Clinical Review; Table 2, page 18)

Study AA24171 was previously reviewed under NDA 22032 in support of Prilosec OTC and demonstrated bioequivalence between Omeprazole DR, 20 mg, OTC to Prilosec, 20 mg, OTC tablets (listed drug). Therefore, Study AA24171 will not be reviewed here (refer to clinical pharmacology review in the original submission of NDA 22032 for details of this study.

For NDA 209400, Studies 150075 and 150076 were extensively reviewed by Jie Cheng, Ph.D., Division of Clinical Pharmacology 3, Office of Nonprescription Products (ONP). Dr. Cheng concluded that the Sponsor's application was "acceptable for approval from a clinical pharmacology standpoint." Dr. Cheng continued, "The proposed new formulation was bridged to Prilosec 20 mg via two relative BA/BE studies that demonstrated bioequivalence between the proposed omeprazole ODT, 20 mg, OTC and the approved omeprazole DR, 20 mg, OTC and bioequivalence between the omeprazole DR, 20 mg, OTC and Prilosec, 20 mg, OTC tablets (Listed drug)."

The study design and results of Studies 150075 and 150076 will be briefly described below. For further details, see Dr. Cheng's Clinical Pharmacology Review (26 May 2017).

Study 150075

Study 150075 was a single-center, randomized, open-label, 4-way crossover bioequivalence study of omeprazole delayed-release orally disintegrating tablet 20 mg and omeprazole delayed-release tablet 20 mg (reference) in 48 healthy subjects to compare the rate and extent of absorption of Omeprazole Delayed-Release Orally Disintegrating Tablet placed on the tongue and administered without (Test 1) or with water (Test 2), or given as a tablet with water

(Test 3), versus Omeprazole Delayed-Release Tablet (Reference), under fasting conditions. The treatment phases were separated by washout periods of seven days. During each treatment phase, frequent pharmacokinetic blood sampling was obtained from pre-dose to 12 hours post-dose. Dr. Cheng reported that the sampling time was acceptable as the half-life of omeprazole is 0.5-1 hour.

Study Results:

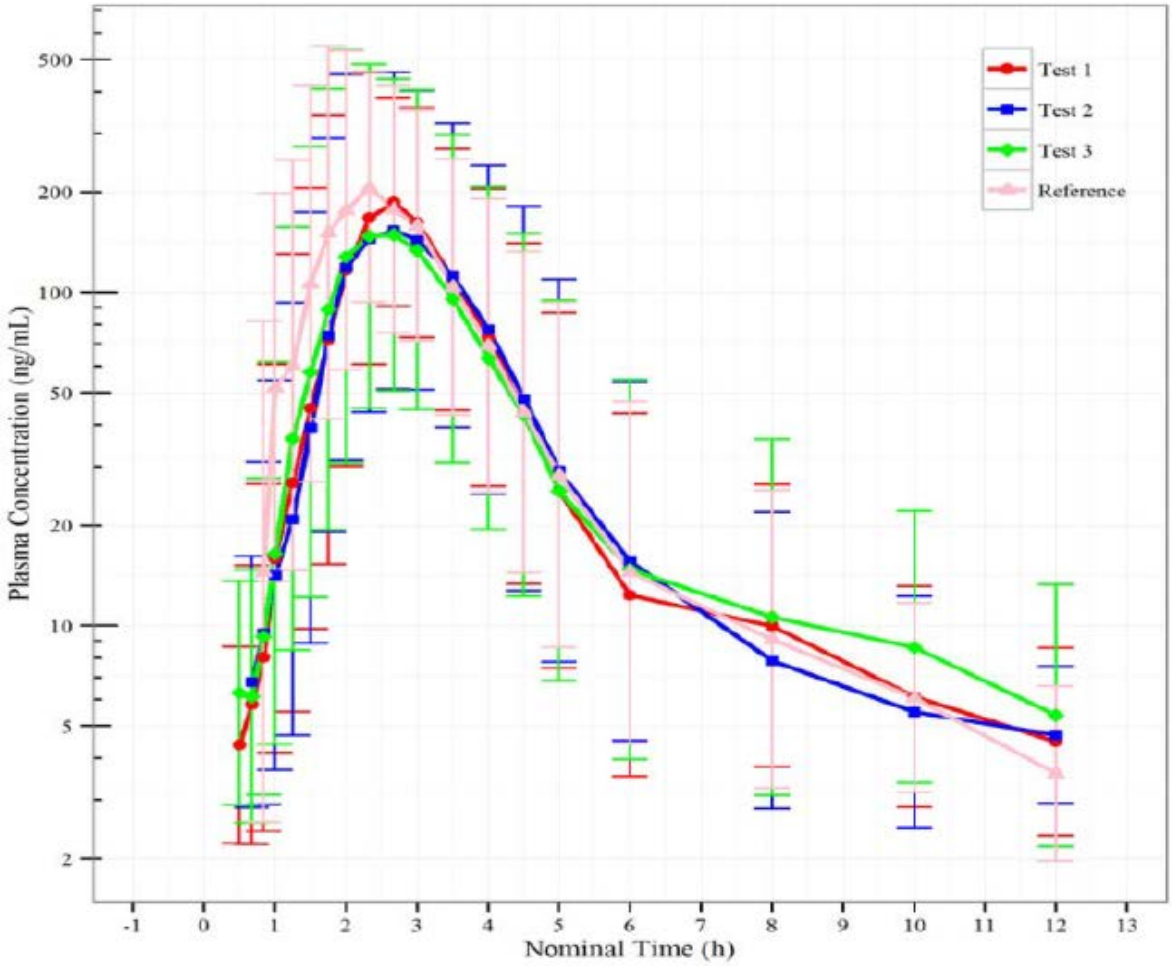
The results of Study 150075 demonstrated that omeprazole ODT is bioequivalent to omeprazole DR tablet under fasting conditions. The 90% CI for the ratio of the geometric means of AUC_{0-t}, AUC_{inf} and C_{max} were within the bioequivalence acceptance criteria of 80-125%, as shown in **Table 3** below. In addition, the bioequivalence was demonstrated between ODT swallowed with water or ODT swallowed whole and Omeprazole DR swallowed whole with water, as shown in the **Table 3** and **Figure 3** below. Thus, the ODT tablet can be administered with or without water, allowed to dissolve on the tongue, or swallowed whole.

Table 3: Relative Bioavailability of Omeprazole ODT Tablets after Administration by Different Methods Compared to Omeprazole DR after Administration as Whole Tablet (Dr. Cheng's Analysis*)

	PK Parameter	Test/Reference	90% C.I.	
Dosing method for omeprazole ODT (Test)		(% Ratio)	Lower	Upper
Disintegrate on the tongue and swallowed without water	C_{max}	99.99	89.90	111.21
	AUC_{0-t}	97.85	92.64	103.34
	AUC_{0-inf}	96.89	91.90	102.16
Disintegrate on the tongue and swallowed with water	C_{max}	99.86	89.79	111.07
	AUC_{0-t}	95.96	90.86	101.35
	AUC_{0-inf}	95.13	90.23	100.30
Swallowed whole with water	C_{max}	103.21	92.76	114.83
	AUC_{0-t}	97.70	92.49	103.20
	AUC_{0-inf}	96.03	91.04	101.30

*There were slight deviations of values between the sponsor's analysis and Dr. Cheng's analysis. However, Dr. Cheng reports that the overall conclusion is consistent between analysis by the sponsor and Dr. Cheng.
(Electronically copied and reproduced from Dr. Cheng's Clinical Pharmacology Review; Table 4, page 6)

Figure 3: Mean (SD) Omeprazole Plasma Concentration-Time Profile (Semi-log)



Test 1: Omeprazole ODT allowed to disintegrate on the tongue and swallowed without water.
Test 2: Omeprazole ODT allowed to disintegrate on the tongue and swallowed with water.
Test 3: Omeprazole ODT swallowed whole with water.
Reference: Omeprazole DR swallowed whole with water.

Study 150076

Study 150076 was a single-center, randomized, single-dose, open-label, 2-way crossover, comparative bioavailability, food-effect study of omeprazole delayed-release orally disintegrating tablet 20 mg. The objective was to assess the effect of food on the pharmacokinetics (PKs) of Omeprazole DR ODT 20 mg administered as 1 x 20 mg delayed release orally disintegrating tablet under fasting and fed conditions. The treatment phases (fasting and fed) were separated by a washout period of seven days. Pharmacokinetic blood sampling was performed frequently up to 24 hours post-dose in each period.

Per protocol, Asians were excluded from the study due to a potential inclusion of CYP2C19 poor metabolizers as CYP2C19 deficiency is more prevalent in Asians than other races, CYP2C19 is the major enzyme that metabolizes omeprazole. Dr. Cheng reported that in studies of single omeprazole doses, an approximate four-fold increase in AUC was noted in Asian subjects compared to Caucasians. Dr. Cheng concluded that “It is acceptable to exclude

subjects of Asian origin to reduce the variability of this bioequivalence study although ideally genotyping should have been used for exclusion of CYP2C19 poor metabolizers."

Study Results:

The results of the study demonstrated that food significantly affects the bioavailability of omeprazole ODT. The rate and extent of absorption were significantly decreased when omeprazole ODT was administered after food. As shown in the **Table 4** below, the AUC_{0-t} and AUC_{inf} were decreased by approximately 21.8% and 19.2%, respectively, under fed conditions. There was also a decrease (56%) in C_{max}. T_{max} was also delayed by about 2 hours in the fed state.

Table 4: Food Effect on Omeprazole ODT Bioavailability in Study 150076*

Pharmacokinetic Parameter	Fed (A)	Fasting (B)	Fed (A) vs. Fasting (B) Geometric Mean Ratio (90% CI)
C_{max} (ng/mL)	230.28±174.22	456.86±338.52	44.02% (32.40%-59.82%)
T_{max} (h)	4.50±3.66	2.17±0.88	--
AUC_{0-t} (ng·h/mL)	836.73±1238.76	1108.81±1459.17	78.20% (69.11%-88.48%)
AUC_{inf} (ng·h/mL)	904.36±1264.60	1072.18±1370.91	80.20% (70.02%-91.86%)

*Analysis by Dr. Cheng
(Electronically copied and reproduced from Dr. Cheng's Clinical Pharmacology Review; Table 8, page 9)

The sponsor proposed labeling the product to be taken before meals in the morning. Prilosec labeling states to take Prilosec at least 1 hour before a meal, and the Omeprazole DR labeling states to "Swallow 1 tablet with a glass of water before eating in the morning." Therefore, Dr. Cheng concluded that the proposed labeling language "Take tablet before eating in the morning" is consistent with those in the labeling of Prilosec and omeprazole DR. I concur.

Conclusions and Labeling Recommendations

Dr. Cheng concluded that "The proposed language of dosing method 'Place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.' is acceptable. The systemic exposure (C_{max} and AUC) following administration of omeprazole ODT swallowed with or without water or ODT swallowed whole with water was not significantly different amongst the dosing methods and from that of Omeprazole DR. In PK studies, the ODT disintegrated on tongue without water. The proposed dosing method of 'take 1 tablet before eating' is acceptable as high fat meal delayed the T_{max} and decreased the systemic exposure to omeprazole. In addition, the proposed label of 'Do not take this medicine with alcohol' is acceptable."

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The efficacy of omeprazole for the proposed OTC indications has been previously demonstrated for approval of the original NDA for the listed drug, Prilosec OTC® (omeprazole magnesium delayed release tablet; NDA 21229, AstraZeneca). Pharmacokinetic assessment is adequate to demonstrate an acceptable pharmacokinetic "bridge" to the listed drug (See **Section 5** above). Therefore, no further efficacy data is needed.

8. Safety

Safety review was conducted by Ryan Raffaelli, M.D., Medical Officer, Division of Nonprescription Drug Products. Dr. Raffaelli's review included an overall assessment of safety data from the two new bioequivalence studies (Studies 150075 and 150076) submitted by the Sponsor and described in **Section 5** above, as well as a review of postmarketing data from other marketed omeprazole and PPI drug formulations. The Sponsor submitted a revised postmarketing safety assessment in the 120-day safety update of January 6, 2017.

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, 118,641 subjects have been exposed to the drug in clinical trials since 2012 with doses up to 40 mg and for durations of several years with more than 32 million patient years' exposure to omeprazole. The 20 mg dose has been approved for OTC marketing status since 2003 with a safety profile supporting continued marketing for the proposed indication. Therefore, the Sponsor intends that the two new trials submitted in this application support extrapolation of safety under a 505(b)(2) application.

8.1 Safety in Clinical Trials

In the two new trials submitted with this application (Studies 150075 and 150076), there were no deaths and no serious adverse events (SAEs) reported. One subject discontinued after a single dose in the first test period due to personal reasons. In total, 68 treatment-emergent adverse events (AEs) were reported by 30 subjects who received one dose of study drug. As shown in **Table 5** below, more subjects (N=14) reported AEs (N=24) after taking the test product without water (Study 150075; Treatment A). Overall, the most common AE was headache. 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 of Study 150076. One subject reported one AE as moderately severe (nausea), while the remaining AEs were mild.

Table 5: Most Frequent (Reported by at least two subjects in any treatment group) Treatment-Emergent AEs by Treatment Arm (Combined Overall Safety Population of Studies 150075 and 150076)

Adverse Event	Treatment Group (Number of subjects dosed)				
	A (N=66)	B (N=48)	C (N=47)	D (N=47)	E (N=18)
Diarrhea	2 (3.0%)	1 (2.1%)	2 (4.3%)	0	0
Nausea	1 (1.5%)	2 (4.2%)	0	1 (2.1%)	1 (5.6%)
Product taste abnormal	7 (10.6%)	1 (2.1%)	0	2 (4.3%)	0
Nasopharyngitis	0	0	1 (2.1%)	0	2 (11.1%)
Headache	5 (7.6%)	2 (4.2%)	3 (6.4%)	4 (8.5%)	2 (11.1%)

Treatment A (Test)= Omeprazole 1 x 20 mg delayed-release orally disintegrating tablet allowed to disintegrate on the tongue and swallowed without water under fasting condition.
Treatment B (Test)= Omeprazole 1 x 20 mg delayed-release orally disintegrating tablet allowed to disintegrate on the tongue and swallowed with water under fasting condition.
Treatment C (Test)= Omeprazole 1 x 20 mg delayed-release orally disintegrating tablet swallowed whole with water under fasting condition.
Treatment D (Reference)= Omeprazole DR (NDA 022032), 1 x 20 mg delayed-release tablet swallowed with water under fasting condition.
Treatment E (Test)= Omeprazole 1 x 20 mg delayed-release orally disintegrating tablet allowed to disintegrate on the tongue and swallowed without water under fed condition.
Modified from Sponsor's submission: Integrated Summary of Safety, NDA 209400; Table 9, pages 37-38

In Study 150075, although the total number of subjects who reported treatment-emergent AEs (TEAEs) and the number of TEAEs following the administration of Treatment A were higher than following administration of Treatments B, C, and D, there were no relevant differences between each treatment group with the exception of "product taste abnormal" which was reported for seven subjects following administration of Treatment A, but for only one subject following administration of Treatment B and two subjects following administration of Treatment D. According to the Sponsor, "this was predictable as Treatment A was the only treatment administered without water."

Clinical laboratory tests (chemistry, hematology, and urinalysis) were performed at each change over period and at study exit and were all within normal limits. Vital signs at screening were acceptable, and electrocardiogram measurements at screening and at study exit were all normal.

All subjects underwent full oropharyngeal assessments (palatal, sublingual, and buccal areas) by physicians or registered nurses 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 combination of signs) and inquiry about history of oral discomfort. All subjects had a Grade 0 (normal mucosa) at every assessment. Dr. Raffaelli noted in his review that there was a three day washout period between test doses in Study 150075 and a seven day washout between doses in Study 150076. Therefore, there was no testing of a period with the same duration as the proposed treatment length for OTC use (14 days). However, Dr. Raffaelli concluded that "the lack of any findings in these, albeit small (six single intermittent doses of test product), studies is consistent with other PPI ODTs, supports safe use for the proposed labeled duration of 14 days."

CDTL Comments: The Sponsor's assertion that, in Study 150075, the increased frequency of the AE, "product taste abnormal" in Treatment A (product allowed to disintegrate on the tongue and swallowed without water) compared to other treatments was predictable is reasonable. I agree that both formulations appear to have been well-tolerated in the two clinical trials and that no relevant differences in safety profiles were observed among the preparations. I also agree with Dr. Raffaelli's conclusion that even though the studies did not address safety over the entire proposed OTC treatment period (14 days), the AE profile in these studies is consistent with other OTC PPIs and supports safe use for the proposed duration of 14 days.

8.2 Postmarketing Safety

The following databases were utilized by the Sponsor to support safety of omeprazole in the OTC setting:

- Sponsor's pharmacovigilance database
- FDA Adverse Event Reporting System (FAERS)
- National Poison Data System (NPDS)
- World Health Organization Vigibase (WHO)
- Drug Abuse Warning Network (DAWN)

The Sponsor notes that the FAERS data identify use for mostly prescription only indications. In addition, data from NPDS and DAWN (data collection terminated in 2011) pertain to PPIs as a class.

Sponsor's Database

The Sponsor conducted a review of its pharmacovigilance database covering a period from 2008-2016. In total, it found 5650 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 (the Sponsor estimated (b) (4) 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%), as shown in the **Table 6** below.

Table 6: Adverse Events by System Organ Class (SOC), (≥ 2.0% of Total (N=5650))

SOC	Serious AE No. (% SOC total)	Nonserious AE No. (% SOC total)	Total N (%)
General disorders and Administration site conditions	45 (2.6)	1691 (97.4)	1736 (**30.7**)
Gastrointestinal disorders	48 (3.0)	1585 (97)	1633 (**28.9**)
Nervous system disorders	47 (9.8)	448 (90.2)	495 (**8.8**)
Skin and Subcutaneous tissue disorders	20 (4.9)	379 (95.1)	399 (**7.1**)
Investigations	21 (8.2)	245 (91.8)	266 (**4.7**)
Musculoskeletal and Connective tissue disorders	27 (10.7)	232 (89.3)	259 (**4.6**)
Respiratory, Thoracic and Mediastinal disorders	22 (9.8)	209 (90.1)	231 (**4.1**)
Psychiatric disorders	12 (9.2)	123 (90.8)	135 (**2.4**)
Injury, Poisoning and Procedural Complications	21 (19.6)	92 (80.4)	113 (**2.0**)

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

FAERS

The Sponsor searched the FAERS database for the period from 2008 through March 2016 and captured 114,016 AEs from 20,877 subjects. A total of 3441 subjects (16.5%) reporting 11,198 AEs (9.8%) specifically identified OTC products. Dr. Raffaelli notes that, for those subjects reporting AEs not specifically identified as related to OTC products, the AEs can be linked to more serious prescription (Rx) conditions (e.g., gastric ulcer, heliobacter disease, gastroesophageal reflux disease). Where data were provided, 5.9% of subjects (N=1095) reported taking 20 mg per day, the approved OTC dose strength of omeprazole. The Sponsor notes that patients reporting taking 10 mg doses listed 3.3 events on average, whereas patients 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 AEs reported include headache, abdominal pain, constipation, diarrhea, and flatulence. Common AEs for OTC products are shown in **Table 7** below. Prilosec OTC (**NDA**

21229) was implicated in 6621 AEs and a generic delayed release product (**ANDA 78878** was implicated in 1303 AEs.

Table 7: OTC Users Reporting Common Adverse Events; >4% of Total (N=3441)

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

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Dr. Raffaelli points out that the Sponsor provided no further details on the "Incorrect administration – duration" or "Inappropriate schedule" AEs by Preferred Term. Dr. Raffaelli surmises that, most likely, consumers use the OTC product for Rx indications at higher doses and for longer treatment periods than the DFL labels allow. To test his theory, Dr. Raffaelli conducted a quick FAERS search to review the narratives of such reports. Dr. Raffaelli found that, since 2012, a five year period, there were 538 reports associated with "omeprazole," "omeprazole magnesium," as single and combination ingredient products, and these two PTs. As Dr. Raffaelli 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. Dr. Raffaelli notes that it is unclear why that decision is considered an AE categorized as "incorrect administration." The serious cases, a small 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 Sponsor 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. Dr. Raffaelli reports that no new safety issues were identified and findings were consistent with those described in the FAERS database.

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 Sponsor notes that there are no safety signals identified.

National Poison Data System

Data was collected from 2008 through November 2016 from 57 poison control centers across the U.S. and includes 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 Sponsor 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.

8.3 Special Safety Topics

Hypomagnesemia

In March 2011, FDA communicated the risk of hypomagnesemia with long-term use of PPIs or when PPIs are taken with concomitant drugs that may potentiate hypomagnesemia (e.g., digoxin, certain diuretics). Five cases of low serum magnesium were reported in the Sponsor's database with its delayed release tablet, and only three reported duration of use (all longer than the Drug Facts allows). In addition, 74 cases associated with use of 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).The correlation between duration of treatment and hypomagnesemia is in-line with the FDA safety communication of 2011 that states that prolonged use of prescription PPIs may cause low magnesium levels. Thus, it is likely that taking OTC omeprazole carries little risk of developing hypomagnesemia when used according to package directions.

Cardiac Symptoms

The Sponsor reported that 35 adverse events associated with cardiac disorders were received during 2008- May 2016, none of which were associated with hypomagnesemia. There were 22 cases of palpitations. 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).

CDTL Comments: It appears that cardiac disorders are rare adverse events. It should be noted that in May 2015, the Division of Epidemiology-I (DEPI-I) conducted a review based on

*reports in the literature of possible association of PPIs with myocardial infarction (MI). However, DEPI-I concluded that the studies have significant limitations as a result of which the studies failed to support a causal association between PPIs and major adverse cardiovascular events. DEPI-I recommended continued surveillance of the medical literature and routine pharmacovigilance for adverse cardiovascular outcomes with PPI use. Currently, there is no conclusive data to suggest an association between PPI use and cardiovascular events. In her Clinical Review for Nexium 24HR capsules (**NDA 204655**; February 19, 2014), Dr. Jane Filie provided plausible explanations for any such association. First, patients with underlying cardiovascular disease who concomitantly have GERD or dyspepsia may be taking PPIs. Second, patients may mistakenly attribute epigastric discomfort to gastrointestinal cause when the symptoms are actually of cardiac etiology. I agree with Dr. Filie. 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." Therefore, there is no need for changes to DFL regarding this issue.*

Fractures and Osteoporosis

In the databases, there were10 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.

CDTL Comments: 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. Fracture risk does not appear to be associated with short term PPI use. The DFL is intended to 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. Consumers are warned to seek medical device if they 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 Sponsor's database.

CDTL Comment: The proposed DFL includes the warning to stop use and see a doctor if you get diarrhea. This is consistent with the DFL of other PPIs and adequately addresses this issue.

Misuse Cases

The Sponsor identified a total of 1704 reports of misuse. 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 greater than 14 day treatment duration. Regarding pediatric events by System Organ Class (SOC), Injury, Poisoning and Procedural complications were most common with 10 events, mostly represented by accidental exposures.

CDTL Comments: No new misuse concerns which would necessitate any changes to the proposed DFL were identified.

Drug-Drug Interactions

In general, relevant drug-drug interactions are already identified in labeling. With regard to postmarketing safety experience describing drug interactions, the sponsor identified 28 reports associated with its delayed release tablet formulation. Only three were serious and none were unlabeled or raised a 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.

CDTL Comments: In his review, Dr. Raffaelli notes that, "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." I agree with Dr. Raffaelli and recommend no further revisions to OTC labeling regarding drug-drug interactions at this time.

Acute Interstitial Nephritis

In his review, Dr. Raffaelli noted that there have been reports of acute interstitial nephritis (AIN) associated with the use of PPIs. In 2006 through August 2009, New Zealand investigators[2] followed a national cohort of 572,661 patients with no history of kidney disease

[2] Blank M-L, L Parkin, C Paul, P Herbison, 2014, A Nationwide Nested Case-control Study Indicates an Increased Risk of Acute Interstitial Nephritis with Proton Pump Inhibitor Use, *Kidney Int*, 86: 837-844.

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. 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." Risks appeared to be 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. However, eleven cases described AIN diagnosis after ≤ 14 days' use. Cases were frequently clouded by co-morbidities, concomitant medications and age where renal toxicity is a risk.

Prescription labeling for omeprazole contains a section entitled "Acute Interstitial Nephritis" under Warnings and Precautions which states, "Acute interstitial nephritis has been observed in patients taking PPIs including Omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Omeprazole if acute interstitial nephritis develops."

CDTL Comments: Dr. Raffaelli points out in his review that, although there is a classic triad of signs and symptoms of AIN (rash, fever, and eosinophilia), they are frequently not present and symptoms are frequently nonspecific (nausea, malaise). Thus, Dr. Raffaelli concludes that it is not clear how effective a warning regarding the risk of AIN would be to OTC consumers, and I agree. It appears that PPI-associated AIN is a rare, idiosyncratic event with nonspecific symptoms; therefore, changes to OTC labeling to try to convey this risk would likely not be helpful. It is noteworthy that a Citizen Petition (Docket No. FDA-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. In response to the Citizen Petition (October 31, 2014), revisions were made to prescription PPI labeling only, and FDA concluded that the symptoms of AIN are "indistinguishable from relatively minor viral episodes that would not otherwise require discontinuation" of a PPI. I agree that including a warning would likely confuse OTC consumers.

Cutaneous and Systemic Lupus Erythematosus

A search of the WHO database identified 48 reports of PPI use associated with cutaneous lupus erythematosus (CLE). In FAERS, 43 case reports were identified. None of these cases identified an OTC omeprazole product, use of an OTC dose, or use over a short duration. A minimum of three weeks PPI use prior to onset of symptoms was reported in the literature of several of these cases. Therefore, the Sponsor concluded that "no additional warning will be added to the labeling of the proposed product." It does not appear that the Sponsor performed a search for systemic lupus erythematosus.

CDTL Comments: In his review, Dr. Raffaelli noted that while prescription labeling in Europe has been revised to reflect the apparent association, CLE appears to be rare, and Dr. Raffaelli reported that FDA continues to monitor these cases. Specifically, a Tracked Safety Issue (TSI 1455) was opened on 2 July 2015, and subsequent reviews were conducted by the Division of Gastroenterology and Inborn Errors Products (DGIEP) and the Division of Pharmacovigilance I (DPV-I). In her summary review [Tracked Safety Issue (TSI) Integrated Review Memorandum (6 April 2017)], Dr. Valerie Pratt, Deputy Director for Safety, DNDP, wrote, "DNDP concurs with OSE and DGIEP that patients and consumers should be informed of the risk [of] cutaneous and systemic lupus erythematosus. Nonprescription PPI class labeling should be updated to reflect this information as well." Dr. Pratt recommended the following revision to the "Warnings" section of nonprescription PPI Drug Facts labels:

Following the subheading, "Stop use and ask a doctor if", add the following bullet after the bullet that reads "you get diarrhea":

- *You develop a rash or joint pain*

A CBE0 letter conveying this recommendation was issued to ***NDA 21229*** *Prilosec OTC, the Listed Drug for this application, on 6 April 2017.*

Vitamin B12 Deficiency

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.

8.4 Literature References

The sponsor searched for relevant safety literature published over a five-year duration (2011-2016) and identified 31 studies. All of the studies described subjects taking up to 40 mg omeprazole for treatment periods longer than 14 consecutive days. Only one study[3] evaluated OTC dosing of omeprazole in a small (N=40) randomized trial comparing omeprazole to Prevacid 24HR® (lansoprazole). In this study, there were no serious AEs or other events

[3] 9 Miner Jr PB, LA McKean, RD Gibb, GN Erasala, DL Ramsey, JW McRorie, 2010, Omeprazole-Mg 20.6 Control of Gastric Acid: A Comparison of Over-the-counter Doses of Proton Pump Inhibitors, *Aliment Pharmacol Ther*, 31: 846-851.

resulting in discontinuation. Most AEs reported were mild in severity and non-specific or labeled, e.g., abdominal pain and headache.

9. Advisory Committee Meeting

No Advisory Committee meeting was held or deemed necessary for this application.

10. Pediatrics

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 in 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. On June 7, 2017, the proposed pediatric waiver was again discussed at the PeRC meeting, and PeRC confirmed its agreement with the proposed full pediatric waiver.

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.

*CDTL Comments: I concur with the request for a waiver of pediatric studies. FDA has waived pediatric studies for the other PPIs because, as stated by Dr. Leonard-Segal in her Summary Review of OTC lansoprazole (**NDA 22327**; May 11, 2009), "it would not be safe to use this medication OTC in the pediatric population since the underlying causes for heartburn in children should be evaluated by a healthcare professional." Importantly, the proposed labeling will state "for adults 18 years of age and older" and will include a bullet stating, "children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition." This is consistent with other PPI DFLs.*

11. Other Relevant Regulatory Issues

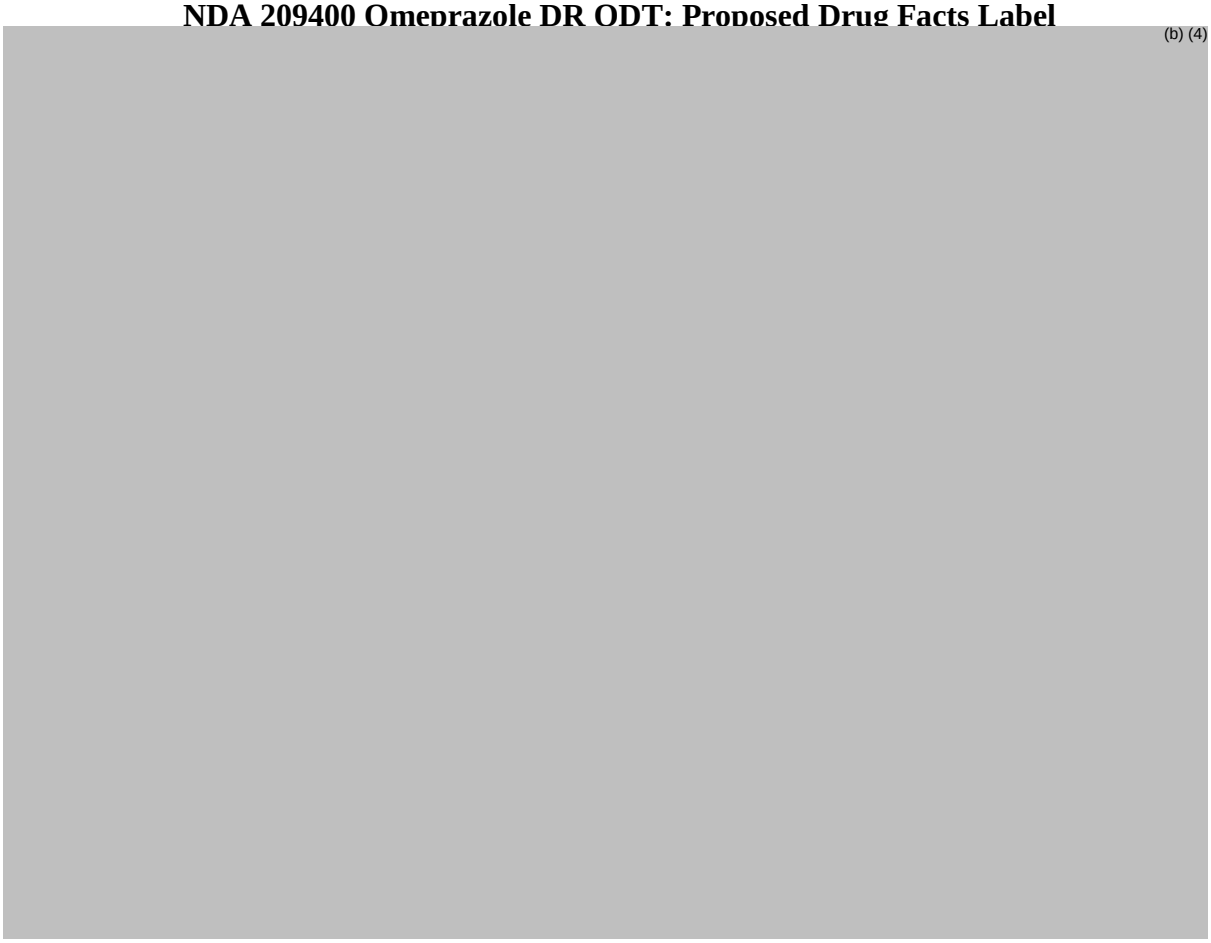
This electronic submission was of high quality, well organized, and easy to navigate. The pharmacokinetics (PK) studies conducted to support this application were conducted at (b) (4) Trials were conducted in compliance with 21 CFR 56 and current Good Clinical Practice (cGCP) Guidelines as required by the International Conference on Harmonization, the Declaration of Helsinki (2000), Standard Operating Procedures of the Sponsor, and the ethical principles of the Directive 2001/20/EC (Europe). The Sponsor 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.

12. Labeling

Labeling review was conducted by Mary R. Vienna, RN, MHA, DNDP, ODE IV. In general, the proposed language in the Drug Facts Label (DFL) and Principal Display Panel (PDP) was nearly identical to either that of the listed drug (**NDA 21229**) or to that of an approved OTC PPI (**NDA 208025**) of the same dosage form. A sample of the proposed DFL and PDP are shown below:

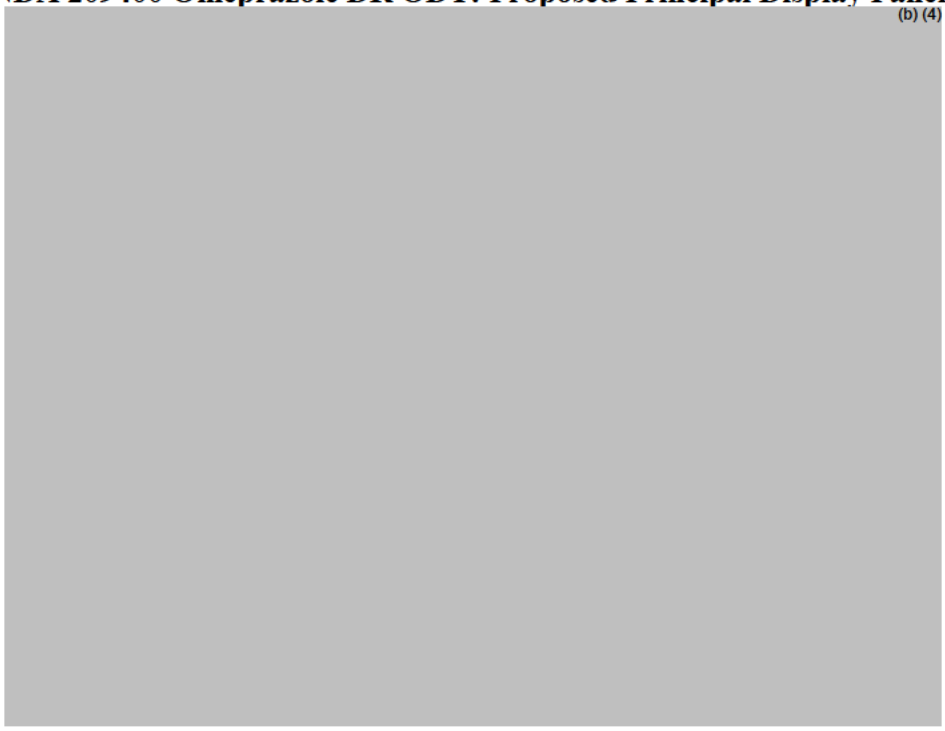
NDA 209400 Omeprazole DR ODT: Proposed Drug Facts Label

(b) (4)



NDA 209400 Omeprazole DR ODT: Proposed Principal Display Panel

(b) (4)



For Drug Facts labeling review, Ms. Vienna compared the proposed labeling to that of two other approved applications: **NDA 22032** (omeprazole 20 mg) for the active ingredient section of the DFL because the active ingredients are identical; and **NDA 208025** (lansoprazole 15 mg) for aspects of the ***Directions*** section of the proposed label unique to the orally disintegrating tablet dosage form, as **NDA 208025** is the only approved OTC PPI with the orally disintegrating tablet dosage form. For details of her review and recommendations, please see her reviews (Labeling Review for Omeprazole Delayed-Release Orally Disintegrating Tablets; May 23, 2017, and Amended Labeling Review for Omeprazole Delayed-Release Orally Disintegrating Tablets; June 12, 2017). Important points from her reviews include the following:

- The image of the pink tablet on the lower right corner of the PDP (see PDP above) includes a white smear to the right of the tablet which distorts the tablet image and affects the accuracy of the "Actual size" statement which appears below the tablet. Ms. Vienna recommends revising the graphic image to be similar to the orally disintegrating tablet graphic approved for the sponsor's NDA 208025 S-003, approved on May 9, 2017.
- Under the ***Stop use and ask a doctor if*** section (see DFL above), Ms. Vienna recommends adding the bullet "you develop rash or joint pain" after the bullet that reads "you get diarrhea." (b) (4)

  See **Section 8.3** above.
- The statement "(b) (4) for the 2-count blister foil is not acceptable. Ms. Vienna points out that while the 14-count carton used with the 7- and

14-count blister labels does contain a 14-day course of treatment, the 2-count blister label does not. Therefore, Ms. Vienna recommends revising the statement for the 2-count blister to read "First two doses of a 14-day course of treatment" as approved for the 2-count blister foil for other PPIs (e.g. NDA 204655).

CDTL Comments: Complete labeling comments and recommendations were sent to the sponsor on May 24, 2017. The sponsor submitted revised labeling on June 2, 2017 which appears to have incorporated all of the FDA recommendations, as shown below. Ms. Vienna recommends approval of the revised labeling, and I concur.

NDA 209400 Omeprazole DR ODT: Revised DFL (June 2, 2017)

Drug Facts

Active ingredient (in each tablet) — **Purpose**
Omeprazole 20 mg ..... Acid reducer

Use
- treats frequent heartburn (occurs *2 or more* days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Warnings

Allergy alert: do not use if you are allergic to omeprazole

Do not use if you have:
- trouble or pain swallowing food, vomiting with blood, or bloody or black stools
- heartburn with **lightheadedness, sweating or dizziness**
- chest or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**

These may be signs of a serious condition. See your doctor.

Ask a doctor before use if you have:
- had heartburn over 3 months. This may be a sign of a more serious condition
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are taking:
- warfarin, clopidogrel or cilostazol (blood-thinning medicines)
- prescription antifungal or anti-yeast medicines
- diazepam (anxiety medicine)
- digoxin (heart medicine)
- tacrolimus or mycophenolate mofetil (immune system medicines)
- prescription antiretrovirals (medicines for HIV infection)
- methotrexate (arthritis medicine)

Stop use and ask a doctor if:
- your heartburn continues or worsens
- you need to take this product for more than 14 days
- you need to take more than 1 course of treatment every 4 months
- you get diarrhea
- you develop a rash or joint pain

Drug Facts (continued)

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222).

Directions
- for adults 18 years of age and older
- this product is to be used once a day (every 24 hours), every day for 14 days
- it may take 1 to 4 days for full effect; some people get complete relief of symptoms within 24 hours

14-Day Course of Treatment
- take 1 tablet before eating in the morning
- **do not crush or chew tablets**
- place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.
- take every day for 14 days
- do not take more than 1 tablet a day
- do not use for more than 14 days unless directed by your doctor
- do not take this medicine with alcohol

Repeated 14-Day Course (if needed)
- you may repeat a 14-day course every 4 months
- **do not take for more than 14 days or more often than every 4 months unless directed by a doctor**

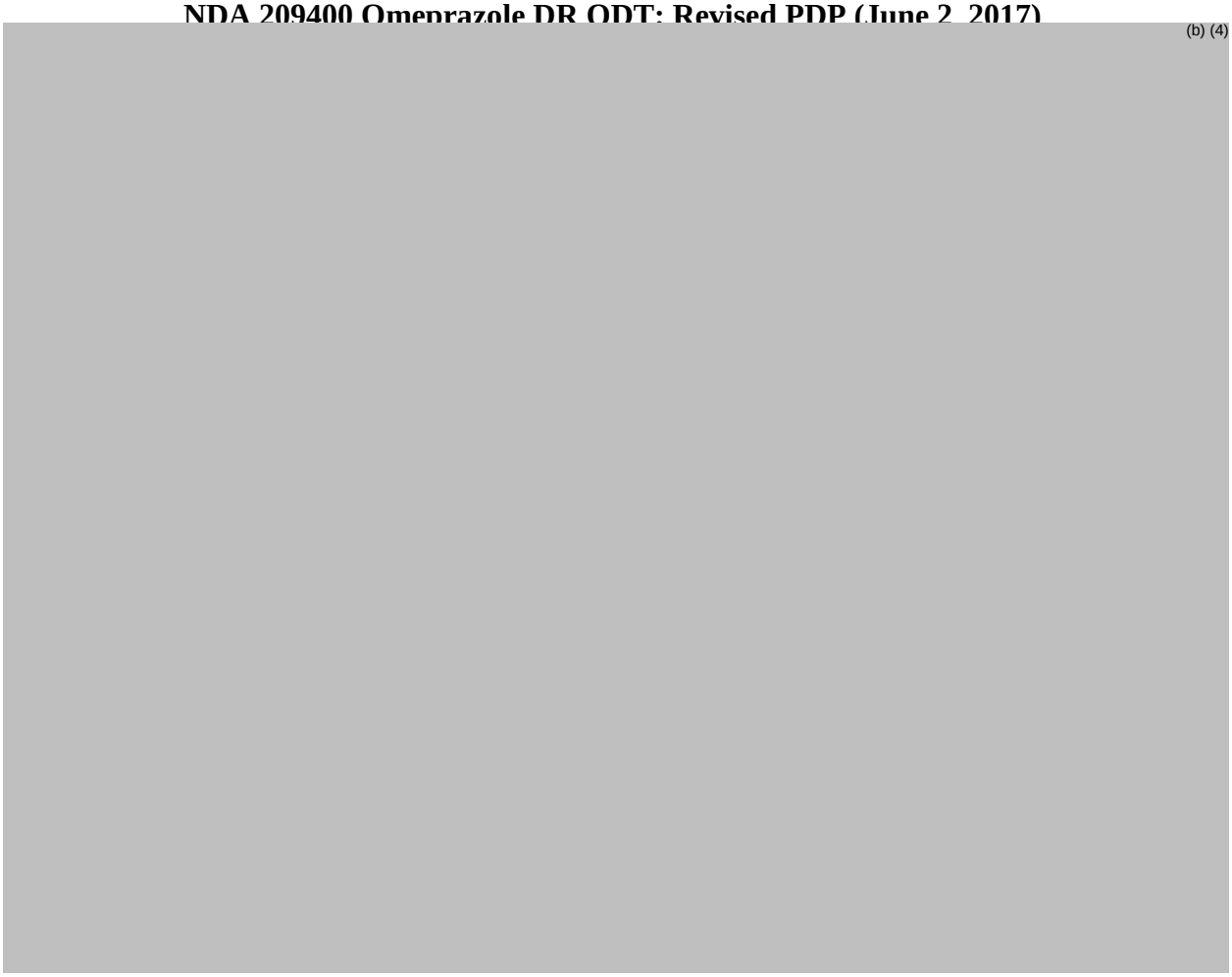
- children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.

Other information
- read the directions and warnings before use
- keep the carton. It contains important information.
- store at 20-25°C (68-77°F); keep product out of high heat and moisture

Inactive Ingredients amino methacrylate copolymer, ascorbic acid, cetyl alcohol, colloidal silicon dioxide, crospovidone, ferric oxide, flavor, hypromellose, hypromellose phthalate, maize maltodextrin, mannitol, microcrystalline cellulose, propylene glycol, silicon dioxide, sodium stearate, sodium stearyl fumarate, sorbitol, sucralose, sugar spheres, talc, titanium dioxide, triethyl citrate

NDA 209400 Omeprazole DR ODT; Revised PDP (June 2, 2017)

(b) (4)



13. Recommendations/Risk Benefit Assessment

I recommend approval for NDA 209400 (omeprazole delayed release orally disintegrating tablet [omeprazole ODT] 20 mg) for the OTC treatment of frequent heartburn (occurs 2 or more days a week) in adults 18 years of age and older. The proposed indication is identical to the approved OTC indication for other marketed formulations of omeprazole at the same dosage strength. The Sponsor has successfully demonstrated a scientific "bridge" from omeprazole ODT to FDA findings of efficacy and safety for the listed drug, Prilosec OTC (NDA 21229). Furthermore, the safety profile is consistent with the safety profile of other omeprazole products and other PPIs. The Sponsor and FDA have reached agreement on labeling which will adequately address safety issues and is consistent with labeling for other OTC PPIs. Omeprazole ODT will provide consumers with a convenient option for OTC treatment of frequent heartburn. The ODT formulation will provide an alternative mode of administration based on consumer preference.

In support of this application, the Sponsor conducted two pharmacokinetic (PK) studies. Study 150075 was a single-center, randomized, open-label, 4-way crossover bioequivalence study of omeprazole delayed-release orally disintegrating tablet

(omeprazole ODT) 20 mg and omeprazole delayed-release tablet (omeprazole DR) 20 mg (reference) in 48 healthy subjects to compare the rate and extent of absorption. The study demonstrated bioequivalence between the proposed product and omeprazole delayed-release tablet and demonstrated that the ODT tablet can be administered with or without water, allowed to dissolve on the tongue, or swallowed whole. Study 150076 was a single-center, randomized, single-dose, open-label, 2-way crossover, comparative bioavailability, food-effect study of omeprazole delayed-release orally disintegrating tablet 20 mg. The results of this study demonstrated that food significantly affects the bioavailability of omeprazole ODT. Therefore, the proposed DFL will state to take "1 tablet before eating in the morning." This is consistent with the DFL directions for other OTC omeprazole products.

The Sponsor relied on Study AA24171 (Omeprazole DR vs. Prilosec ODT) to provide a scientific "bridge" from the proposed product to the Agency's finding of safety and efficacy for the listed drug, Prilosec OTC. This study was previously reviewed under NDA 22032 in support of Prilosec OTC and demonstrated bioequivalence between omeprazole DR, 20 mg, OTC to Prilosec, 20 mg, OTC tablets.

To support safe use in the OTC market, the sponsor provided safety data from the two PK studies, postmarketing experience (2008-2016) for omeprazole and other PPI products, and published scientific literature. Common postmarketing adverse events reported overall included drug ineffective, incorrect dose administration, headache, abdominal pain, constipation, and flatulence. Most events were non-serious (94%), and the reports accounted for a small proportion of the estimated (b) (4) 14-day courses used by consumers over the same 8-year timeframe. In many cases, the AEs were associated with use of OTC PPIs for Rx indications, including higher doses and longer treatment periods. No new safety signals were identified. In the two PK studies, the Sponsor conducted oropharyngeal assessments, and no oropharyngeal irritation was observed. Thus, the safety profile of the proposed product is expected to be comparable to that of the currently marketed omeprazole DR and Prilosec OTC. Agreement has been reached with the Sponsor regarding the contents of the DFL, which is nearly identical to the DFLs for other omeprazole and PPI products. With proper OTC use according to the DFL, the risk-benefit assessment is acceptable.

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/s/

FRANCIS E BECKER
06/13/2017