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APPLICATION NUMBER:

204655Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	Mar 27, 2014
From	Theresa M. Michele, MD Director, Division of Nonprescription Clinical Evaluation
Subject	Division Director Summary Review
NDA/BLA # Supplement #	204,655
Applicant Name	AstraZeneca LP
Date of Submission	May 30, 2013
PDUFA Goal Date	March 30, 2014
Proprietary Name / Established (USAN) Name	Nexium 24 HR/ esomeprazole magnesium
Dosage Forms / Strength	20 mg capsule
Proposed Indication(s)	Treats frequent heartburn (occurs 2 or more days a week)
Regulatory Action	Approval

1. Introduction

AstraZeneca LP (AstraZeneca) submitted this 505(b)(1) new drug application for over-the-counter (OTC) use of Nexium 24 HR (esomeprazole magnesium) 20 mg delayed release capsules to treat frequent heartburn occurring 2 or more days a week. The proposed dose is one 20 mg capsule once daily limited to 14 days of use. As this OTC indication represents a meaningful difference from the prescription indications for esomeprazole magnesium (esomeprazole), this application is not considered an OTC switch, and is not anticipated to affect the marketing status of the prescription product.

The application is based on 2 replicative clinical efficacy and safety trials performed in patients with frequent heartburn. This summary review provides an overview of the application, with a focus on the clinical efficacy and safety trials.

2. Background

Esomeprazole magnesium (esomeprazole) is a proton pump inhibitor (PPI) that functions to stop acid production in the stomach. Esomeprazole was approved in 2001 as a prescription product under NDA 21-153 for the treatment of gastroesophageal reflux disease (GERD), risk reduction of NSAID-associated gastric ulcers, H.pylori eradication, and hypersecretory conditions including Zollinger-Ellison syndrome. The prescription product has a lower dose of 20 mg (the proposed dose for OTC) and a higher dose of 40 mg, both once daily.

Esomeprazole is the S-isomer of omeprazole, a racemic mixture of the S- and R-isomers. OTC omeprazole was approved in 2003 under the trade name Prilosec (NDA 21-229). Other PPIs available OTC (not including generics) are shown in Table 1.

Table 1: OTC PPIs

NDA	Sponsor	Proprietary name	Established name	Year approved
21-229	Astra Zeneca	Prilosec OTC	omeprazole (tablet)	2003
22-032	Dexcel	none	omeprazole (tablet)	2007
22-281	MSD Consumer	Zegerid OTC	omeprazole/sodium bicarbonate (capsule)	2009
22-327	Novartis	Prevacid 24 HR	lanzoprazole	2009
22-283	MSD Consumer	Zegerid OTC	omeprazole/sodium bicarbonate (for oral suspension)	2013

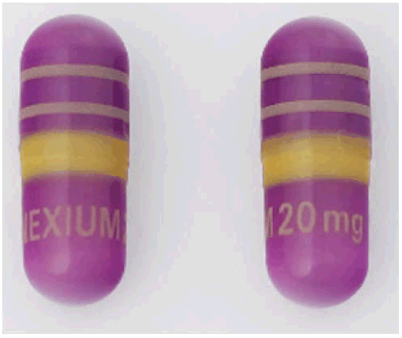
Source: original table by the author

During the development program, FDA provided feedback to AstraZeneca as preliminary responses for a pre-IND meeting (cancelled by the sponsor), an advice letter about the primary efficacy trials for the application, and preliminary responses for a pre-NDA meeting (cancelled by the sponsor). In the Pre-IND comments FDA agreed that consumer studies were not necessary unless there were new elements in the proposed product label and the sponsor's proposed stability studies were acceptable. In general, the development program and labeling were expected to be similar to other approved OTC PPIs.

3. CMC

The drug product proposed for OTC use [redacted] (b) (4) 20 mg capsule [redacted] (b) (4) with [redacted] (b) (4) a gelatin band covering the junction of the cap and base of the capsule, which serves as a tamper-evident seal. A seal of this nature is generally required for OTC capsule products. A picture of the product is shown in Figure 1.

Figure 1: Nexium OTC capsules



Source: NDA 204,655 information amendment dated 19 December 2013

The strength of esomeprazole is [redacted] (b) (4) 22.3 mg of esomeprazole magnesium trihydrate. The drug substance, esomeprazole magnesium trihydrate, is the same as NDA 21-153 (Nexium), which is cross referenced in this NDA. The [redacted] (b) (4) process for the drug product, impurity profile, and container closure were deemed acceptable by the CMC reviewer. The product is packaged in square-shaped bottles containing 14 capsules. The

sponsor intends to market the bottles in 3 different carton configurations containing 1, 2, or 3 bottles per carton.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology and toxicology data for esomeprazole were reviewed under NDA 21-153 for the prescription product. The nonclinical development program for the prescription product was conducted as a bridging program from omeprazole (Prilosec). No new nonclinical data were submitted as part of this application.

During the review cycle for this application, the prescription label for Nexium was updated with new reproductive toxicology data, (b) (4) the pregnancy category (b) (4) C. The risk summary from the prescription label is as follows:

> *There are no adequate and well-controlled studies with NEXIUM in pregnant women. Esomeprazole is the s-isomer of omeprazole. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use.*
>
> *Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole magnesium in rats and rabbits with doses about 57 times and 35 times, respectively, an oral human dose of 40 mg. However, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 33.6 times an oral human dose of 40 mg (see Animal Data). Because of the observed effect at high doses of esomeprazole magnesium on developing bone in rat studies, NEXIUM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus*

The sponsor also notes that that there are two observational studies linking prenatal exposure to PPIs to an increased risk of childhood asthma, and has an observation and a cohort study ongoing at the request of United Kingdom regulatory authorities to investigate this possible association.

Overall, there is nothing in these data that would preclude safe use in an OTC setting. The product will carry the standard pregnancy warning for OTC PPIs “If pregnant or breast feeding, ask a health professional before use.” Based on these considerations, I agree with the conclusions recommending approval reached by the pharmacology toxicology reviewer for this application. We will request that the ongoing asthma studies are submitted to the NDA when available.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this application. Comparative dissolution data, a biowaiver request, and dissolution data were submitted. Based on these data, the biowaiver for the comparison to the prescription product is granted, and the biopharmaceutics reviewer recommends approval, a conclusion with which I concur.

A number of drug-drug interactions are noted on the prescription label for Nexium. An interaction with methotrexate was added as class labeling to prescription PPIs in 2012, noting that concomitant use may elevate levels of methotrexate. To be consistent with this class labeling, this interaction will also be added to Nexium OTC under "Ask a doctor or pharmacist before use if you are taking." Similar class labeling changes for this drug-drug interaction will be requested for all OTC PPI labels.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

7.1. Overview of the clinical program

Some characteristics of the relevant clinical trials that form the basis of review and regulatory decision making for this application are shown in Table 2. In addition, the sponsor references safety data from the prescription program submitted under NDA 21-153.

Table 2: Relevant clinical studies with esomeprazole

ID [Year*]	**Study Characteristics - Patient age, mean (range) - Population - Study design - Study duration**	**Treatment groups**	**N‡**	**Primary endpoint**	**Country**
001 [2011]	- 45 (19-85) yrs - frequent heartburn - parallel group - 14 days	Eso 20mg QD Placebo	168 163	% heartburn-free days	US
002 [2011]	- 42 (18-90) yrs - frequent heartburn - parallel group - 14 days	Eso 20mg QD Placebo	162 158	% heartburn-free days	US

*Year study enrollment ended; ‡Number randomized and received at least one dose
Eso = esomeprazole magnesium; QD = once daily; US = United States

7.2. Design and conduct of the trials

To support the new indication for treatment of frequent heartburn, the sponsor conducted 2 replicative randomized, controlled Phase 3 efficacy and safety trials. These 2 trials ran concurrently, each at 10 centers in the United States.

The trials were randomized, double-blind, placebo-controlled parallel group design comparing esomeprazole 20 mg once daily for 14 days to placebo in 331 and 320 patients with frequent heartburn. The trials included a 7-day placebo run-in period and a 7-day placebo follow-up period in addition to the 14-day treatment period. Patients were required to have heartburn symptoms for at least 2 days per week over the last month, and were excluded if they had a diagnosis of erosive esophagitis, gastrointestinal reflux disease (GERD), or a requirement for continuous dosing of prescription H2-receptor antagonists or PPIs. The primary endpoint was the percentage of heartburn free days over the 14-day period as defined by a heartburn severity

score of zero in a daily patient-reported diary. Secondary endpoints included proportion of patients with heartburn 2 days or less during the 14-day treatment period, percentage of 24-hour days with no heartburn during days 1 through 4, and the proportions of patients with heartburn one day or less during the last 7 consecutive days of treatment, during Week 1, and during Week 2. Standard safety assessments including adverse events (AEs), hematology and chemistry testing, vital signs, and physical examination were also performed.

7.3. Dose selection

The proposed dose of Nexium OTC is 20 mg for the treatment of frequent heartburn. This is the lower of 2 prescription doses (20 and 40 mg). No specific dose selection studies were performed for the treatment of heartburn.

7.4. Efficacy results and conclusions

The clinical program demonstrated that esomeprazole provided a statistically significant increase in the percentage of heartburn-free days compared to placebo. See Table 13.

Table 3: Percentage of heartburn-free days during 14 days of treatment (Full Analysis Set)

Trial	Esomeprazole		Placebo		Treatment Difference[1]		
	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean (SE)	95% CI	P-value
001	168	46.13 (2.24)	163	33.07 (2.26)	13.06 (2.86)	(7.44, 18.68)	<0.0001
002	162	48.00 (1.96)	158	32.75 (1.99)	15.25 (2.73)	(9.88, 20.62)	<0.0001

Abbreviations: CI, confidence interval; LS, least square; SE, standard error
[1]Obtained from ANCOVA with centers and treatment as fixed effects and heartburn frequency during the run-in phase as covariate.; Full analysis set includes all randomized subjects who took at least one dose of treatment and had both a valide baseline heartburn assessment and at least one valid post-baseline assessment.
Note: Missing values for the treatment phase were imputed based on the run-in phase data.
Source: Dr. Sohrabi's DGIEP review, Table 8, adapted from Sponsor's Table 10, page 34, Summary of Clinical Efficacy

This result was robust across a variety of different sensitivity analyses performed both by the sponsor and by the FDA statistics reviewer. Similar results were obtained for the secondary endpoints. These data are supportive of efficacy for esomeprazole for the indication of treatment of frequent heartburn in an OTC setting.

The sponsor requests the labeling claim "(b) (4) may take 1 to 4 days for full effect, (b) (4) I concur with the recommendation from the clinical team in the Division of Gastroenterology and Inborn Errors of metabolism Products (DGIEP) that these results are insufficient to provide substantial evidence of efficacy supportive of this label claim.

8. Safety

8.1. Consumer studies

Because PPIs are a well-established OTC product, label comprehension, self-selection, and actual use studies were neither conducted nor required.

8.2. Clinical safety data

As a PPI, this product is expected to have an adverse event profile consistent with the prescription product and with other products in this class. The prescription label lists the most common adverse events as headache, diarrhea, nausea, flatulence, abdominal pain, constipation and dry mouth.

The 2 clinical trials submitted with this application enrolled 657 patients, of whom 333 received esomeprazole for up to 14 days. There were no on-treatment deaths or serious adverse events in these trials. Of note, however, during the run-in period there was one patient with myocardial infarction and one acute cardiac arrest resulting in death in a patient with nonspecific ST-T wave changes on baseline ECG. While clearly neither of these cardiac events was caused by esomeprazole, the cases highlight the overlap in symptoms of angina and symptoms of heartburn. Although there is a warning about symptoms of angina in the Drug Facts label, it will be moved to the "Do not use" category to give it greater prominence. Adverse events in the trial were consistent with the known safety profile of esomeprazole.

The sponsor estimates that there have been over 80 million (36 million U.S.) patient exposures to esomeprazole since the launch of the prescription product in 2000 (2001 U.S.). The sponsor submitted post-marketing safety data from 5 different databases, including the sponsor's internal database, the FDA Adverse Events Reporting System, the World Heath Organization Vigibase, the American Association of Poison Control Centers National Poison Data System, and the Drug Abuse Warning Network, as well as a review of the literature. This post-marketing safety review did not demonstrate any new safety signals for esomeprazole and demonstrates that the safety of esomeprazole is generally consistent with that of other PPIs in the class.

Overall, I concur with the clinical review team that the clinical safety of esomeprazole is acceptable for OTC approval.

9. Advisory Committee Meeting

This application was not taken to an Advisory Committee meeting since it is an approved prescription product, it is not a first-in-class switch product, and the indication is not novel for OTC use.

10. Pediatrics

The prescription product Nexium is approved in adults and children down to one month of age. This application triggers PREA due to the new indication. The sponsor requested a full waiver for pediatric studies and has proposed labeling only in adults aged 18 years and older. The waiver was granted because heartburn in children represents underlying causes that should be evaluated by a health professional, precluding safe use in the OTC setting. This approach is

consistent with other PPIs in the class, and was supported by a recommendation from the FDA Pediatric Review Committee (PeRC). Labeling states "children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition."

11. Other Relevant Regulatory Issues

11.1. OSI Audits

Site inspections were not conducted for this application.

11.2. Financial Disclosure

The sponsor submitted acceptable financial disclosure statements. According to the sponsor, there were no sites with reportable payments or financial arrangements.

11.3 Environmental Assessment

An environmental assessment was completed for this product; the Office of Pharmaceutical Science issued a finding of no significant impact (FONSI) for this application.

12. Labeling

12.1. Proprietary name

The sponsor submitted the proposed proprietary name Nexium 24HR, which was reviewed by DMEPA and deemed acceptable.

12.2. Patient labeling

In general, the Drug Facts labeling for esomeprazole resembles that of other products in the class and will contain standard class safety labeling. The majority of warnings included in labeling for the prescription product do not apply to short-term use for the OTC product. The contraindication in patients with known hypersensitivity and warnings for *Clostridium difficile* diarrhea and concomitant use with clopidogrel and a variety of other drug-drug interactions are class labeling that will be included on the product label. As noted previously, the drug-drug interaction with methotrexate is now considered class labeling for prescription PPI products and will be added as well.

The Drug Facts labeling for OTC PPIs has included language about symptoms of angina and myocardial infarction that may overlap and be confused with heartburn symptoms by consumers in the section under "Ask a doctor before use if you have…". However, based on the two serious adverse events that occurred in the run-in period of the clinical trials the language regarding these symptoms will be moved to the "Do not use if you have…" to give the warning greater prominence. This change will be carried into class safety labeling for all OTC PPIs.

Regarding efficacy, as noted previously, the phrase (b) (4) is not supported.

13. Decision/Action/Risk Benefit Assessment

13.1. Regulatory Action

Astra Zeneca has submitted adequate data to support approval of Nexium 24HR (esomeprazole magnesium) for the OTC indication treatment of frequent heartburn at a dose of 20 mg once daily. The regulatory action for this application is Approval.

13.2. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of esomeprazole for the OTC treatment of frequent heartburn in adults. Although esomeprazole has been approved in adults and children as a prescription product since 2001 for the treatment of GERD and other indications, the treatment of frequent heartburn is considered a new indication. To support the new indication for treatment of frequent heartburn, the sponsor conducted 2 replicative randomized, controlled Phase 3 efficacy and safety trials, both of which demonstrated significant improvement in the primary endpoint, percentage of heartburn free days.

The safety profile of the product in clinical trials is consistent with that demonstrated in the prescription setting. Review of post-marketing safety revealed no new safety signals. There were two serious cardiac events in the run-in of these trials, emphasizing the overlap in symptoms between angina and heartburn, which will be reflected by moving these warnings to the "Do not use" section of the Drug Facts Label to give the issue greater prominence. In addition, consistent with the class labeling for prescription PPIs, the drug-drug interaction with methotrexate will be added to the Drug Facts Label.

Overall, the risk-benefit ratio of this product is acceptable for OTC use.

13.3. Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

13.4. Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

THERESA M MICHELE
03/28/2014