CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205103Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 14, 2016
From	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA Supplement #	NDA 205103
Applicant	Aralez Pharmaceuticals
Date of Submission	March 14, 2016
PDUFA Goal Date	September 14, 2016
Proprietary Name / Established (USAN) names	Yosprala (aspirin/omeprazole)
Dosage forms / Strength	Tablet: Delayed Release Aspirin 81 mg or 325 mg; Immediate Release Omeprazole 40 mg
Proposed Indication	YOSPRALA, a combination of aspirin and omeprazole, is indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcer. The aspirin component of YOSPRALA is indicated for: • reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, • reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, • reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, • use in patients who have undergone revascularization procedures (Coronary Artery Bypass Graft [CABG] or Percutaneous Transluminal Coronary Angioplasty [PTCA]) when there is a pre-existing condition for which aspirin is already indicated. The omeprazole component of YOSPRALA is indicated for decreasing the risk of developing aspirin-associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (≥ 55) or documented history of gastric ulcers.
Recommended Action:	Approval

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1. Introduction

A Complete Response (CR) Letter was sent by the Division on December 16, 2014. This resubmission, received March 14, 2016, is a complete response to that letter, and represents the third review cycle for this NDA.

Yosprala Tablets: Yosprala tablets are a multilayer orally administered tablet consisting of:

- an enteric-coated (EC) aspirin core (81 mg or 325 mg), and
- an immediate release (IR) omeprazole 40 mg film coat.

This is intended to allow for a sequential release, first of omeprazole followed by aspirin (b) (4)

Proposed Indication: The proposed indication is as follows:[1]

> "YOSPRALA, a combination of aspirin and omeprazole, is indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcer.
>
> The aspirin component of YOSPRALA is indicated for:
>
> - reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli,
> - reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris,
> - reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris,

[1] The proposed indication is taken from the proposed label in Module 1 of the NDA submission received March 14, 2016.

- use in patients who have undergone revascularization procedures (Coronary Artery Bypass Graft [CABG] or Percutaneous Transluminal Coronary Angioplasty [PTCA]) when there is a pre-existing condition for which aspirin is already indicated.

The omeprazole component of YOSPRALA is indicated for decreasing the risk of developing aspirin-associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (≥ 55) or documented history of gastric ulcers."

Proposed Dosage and Administration: The proposed dosage and administration is once daily.

First Review Cycle: The original 505(b)(2) NDA was submitted by POZEN Inc. on March 25, 2013. The NDA received a CR action on April 25, 2014 because the Office of Compliance had issued an overall "Withhold" recommendation for the (b) (4) manufacturing facility where the aspirin component of the tablet is manufactured.

Second Review Cycle: The NDA was re-submitted by POZEN Inc. on June 30, 2014. The NDA again received a CR action on December 16, 2014 because the Office of Compliance again issued an overall "Withhold" recommendation for the (b) (4) manufacturing facility where the aspirin component of the tablet is manufactured.

It should be noted that the current sponsor (Aralez Pharmaceuticals Inc.) was formed by a merger of the previous sponsor (POZEN Inc.) and another company (Tribute Pharmaceuticals Canada Inc.).[2]

The primary emphasis of this memorandum is on the issues to be resolved in the current review cycle.

2. Background

2.1 Regulatory History

2.1.1 Overview of Regulatory Activity

For regulatory activities prior to the second cycle NDA submission, see the following:

- First Cycle Clinical Review by Zana Marks, dated March 21, 2014, and Addenda dated April 4, 2014, and April 16, 2014.
- First Cycle CDTL Review by Robert Fiorentino dated April 25, 2014
- Second Cycle CDTL Review by Robert Fiorentino dated December 30, 2014

The table below provides an overview of the regulatory activity after the second cycle NDA submission.

[2] https://aralez.com/about/ (accessed August 24, 2016)

Table 1. Pertinent Regulatory History of Yosprala (NDA 205103)*

Date	Event
December 16, 2014	CR Letter issued
January 28, 2015	Teleconference with Sponsor about requirements to resolve issues in CR Letter
March 14, 2016	Current Resubmission for NDA 205103 received

*IND 78,747

2.1.2 Key Comments Communicated to the Sponsor

Key comments communicated to the sponsor included the following:

Complete Response Letter (Second Cycle)

On December 14, 2014, a Complete Response (CR) Letter was issued that included the following:

> "We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.
>
> **FACILITY INSPECTIONS**
>
> 1. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

Teleconference with Sponsor

On January 28, 2015, a teleconference with the Sponsor occurred to discuss the issues in the CR Letter. Key discussion comments from the minutes of the meeting are shown below.

> "Pozen asked if Yosprala can be approved as a safe and effective therapy prior to final resolution of the issues raised in the 483. FDA responded, no. A recommendation of approval is based on multiple disciplinary reviews including Compliance and so the issues raised during the inspection must be adequately addressed."

2.2 Current Submission

This NDA resubmission was received on March 14, 2016. It was classified as a six-month submission with a PDUFA deadline of September 14, 2016. No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines have written review documents. The primary review documents relied upon were the following:

(1) Office of Pharmaceutical Quality (OPQ) Review by Moo-Jhong Rhee dated August 18, 2016 which incorporates the following disciplines/reviews:

(a) Drug Substance (Xavier Ysern)
(b) Drug Product (Zhengfang Ge)
(c) Process (Jingbo Xiao)
(d) Facility (Christina Capacci-Daniel)
(e) Biopharmaceutics (Hansong Chen)
(f) Application Technical Lead (Danuta Gromek-Woods)
(g) ORA Lead (Paul Perdue)

(2) Pharmacology/Toxicology Review by Tamal Chakraborti dated August 5, 2016
(3) Clinical Pharmacology Review by Dilara Jappar dated August 12, 2016
(4) Office of Study Integrity and Surveillance (OSIS) Reviews/Memos:
   (a) Decline to Inspect Memo by Shila Nkah dated August 8, 2016
   (b) Review of Establishment Inspection Report (EIR) by Hasan Irier dated August 19, 2016
(5) Division of Epidemiology (DEPI) Review by Joel Weissfeld, dated July 11, 2016
(6) Division of Pediatric and Maternal Health (DPMH) Reviews:
   (a) Pediatric Review by Erica Radden, dated August 11, 2016
   (b) Maternal Health Review by Christos Mastroyannis, dated August 29, 2016
(7) Labeling Reviews:
   (a) Proprietary Name Review by Sherly Abraham dated May 27,2016
   (b) Label and Labeling Review by Sherly Abraham dated July 28, 2016
   (c) Office of Prescription Drug Promotion (OPDP) Review by Meeta Patel dated August 8, 2016
   (d) Division of Medical Policy Programs (DMPP) Patient Labeling Review by Karen Dowdy dated August 11, 2016

The reviews should be consulted for more specific details of the current application.

3. CMC

The Office of Pharmaceutical Quality (OPQ) Review summarized the quality assessments (including biopharmaceutics assessments) as follows.

3.1 Product Overview

The OPQ Review provided an overview of the product as follows.

3.1.1 Proposed Drug Product:

"Aspirin and omeprazole are the two active pharmaceutical ingredients of the drug product Yosprala™ (81 mg or 325 mg aspirin/ 40 mg omeprazole) tablets. The proposed drug product is an aspirin delayed-release/omeprazole immediate-release tablet. The listed drugs for this 505(b)(2) application are Ecotrin® GSK (aspirin) and Prilosec® AstraZeneca (omeprazole), both are delayed-release.

Aspirin is provided by (b) (4)

(b) (4)

See the chemical structures of aspirin (b) (4) components and omeprazole in the OPQ Review.

3.1.2 Stability:

"The stability of omeprazole in solution is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions. Omeprazole is a racemate of two enantiomers,…"

3.1.3 Drug Product Manufacturing:

"The drug product manufacturing steps use (b) (4) The tablets for both strengths consist of an aspirin core that is coated with (b) (4) film coats (b) (4) as shown below:"

Figure 1 Schematic of Tablet (not to Scale)

(b) (4)

The figure above is taken from the OPQ Review.

3.2 Quality Assessment Overview

The OPQ Review provided an overview of the quality assessment as follows.

3.2.1 Drug Substance

"The drug substance reviewer, Dr. Xavier Ysern, concludes that the quality of 'the described drug substances is deemed acceptable to support their use in the manufacture of the proposed drug product Yosprala™ (81 mg or 325 mg aspirin/ 40 mg omeprazole) tablets as described under Applicant's NDA 205-103'."

3.2.2 Drug Product

"As per Drug Product reviewer, the aspirin mixture supplied [redacted] contains [redacted]"

3.2.3 Stability

"No significant differences have been observed for the real time stability results comparing the drug products using [redacted] aspirin and drug products using [redacted] aspirin (see review #2 in the previous review cycle). Therefore, the proposed 36 months expiration dating period is granted for the drug product stored at USP room temperature condition based on the 36 months long term stability data for the drug products manufactured with aspirin from [redacted] Post-approval stability protocol and commitment are adequate."

3.2.4 Process

"The Process Review states that there are no changes [redacted] The firm provided adequate information for in-process controls and for the commercial scale-up."

3.2.5 Microbiology

"Regarding the Microbiology assessment, the review of the original submission dated 08-Jul-2013 remains adequate for microbial limit specifications for the drug product, as there are no changes in the control of microbial limits in the current resubmission."

3.2.6 Biopharmaceutics

"Biopharmaceutics Review dated 9-Aug-2016 made a recommendation of approval, but ***raised a concern regarding the degradation of omeprazole in the acidic medium of stomach:*** As stated in the review,

> '*The dissolution of Yosprala tablet in acid medium (0.1 N HCl) demonstrated that* [redacted], see graph below:

However, in the addendum dated 17-Aug-2016 to the previous Review (9-Aug-2016), Biopharmaceutics Team states that safety concern in-vivo about these degradants is beyond the Biopharmaceutics purview and is deferred to pre-clinical and clinical teams."

3.2.7 Facilities Review/Inspection

"The Office of Facility and Process has made a final overall manufacturing Inspection 'Approve' recommendation for the facilities involved in this application,…"

3.3 Final Recommendation

The final recommendation/conclusion on approvability by CMC is the following (***emphasis added***):

> "This applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product before the drug administration.
>
> The Office of Facility and Process has made a final overall "Approve" recommendation for the manufacturing inspection of facilities involved in this application.
>
> Labeling and labels are deemed satisfactory from the CMC perspective.

The issue raised by the Biopharmaceutics Review about acid degradation of omeprazole in the stomach is deemed to be beyond the Biopharmaceutics' purview and its safety concern is deferred to Clinical Team, but OPQ will support and cooperate with any post approval investigation on this issue, if it be warranted by the Clinical Team.

Therefore, from the OPQ perspective, this application is recommended for Approval with expiration dating period of 36 months."

The following postmarketing commitment (PMC) is recommended:

Conduct an in vitro study to characterize and quantify the degradants of immediate release omeprazole of Yosprala at various pHs (i.e., pH 1, 1.5, 2, 2.5, 3, 3.5, 4) following a minimum of 1 hour of exposure at 37°C, and evaluate the differences in the profiles across pHs. Submit the chromatograms and a summary of quantitative data generated during the study.

Final Protocol Submission:	01/2017
Study/Trial Completion:	04/2017
Final Report Submission:	06/2017

It should be noted that the issue is appropriate for a PMC instead of a pre-approval requirement because prior clinical experience indicates safety and the issue is a theoretical concern. The drug's safety profile has been adequately assessed in the pre-approval program. However, because this product contains non-enteric coated omeprazole which may be unstable in acidic pH, there is residual uncertainty regarding potential omeprazole degradants in the acidic pH of the stomach. To address this residual uncertainty an in vitro study will be conducted to characterize and quantify the degradants of immediate release omeprazole of Yosprala at various pH ranges (i.e., pH 1, 1.5, 2, 2.5, 3, 3.5, 4) following a minimum of 1 hour of exposure at 37°C and to evaluate the differences in the profiles across the pH range; the applicant should submit the chromatograms and summary of quantitative data generated in the study..

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology Review summarized the nonclinical findings as follows.

4.1 Brief Discussion of Nonclinical Findings

The Applicant did not submit any nonclinical study report in this resubmission.

The Nonclinical Pharmacology/Toxicology Reviewer referred to previous nonclinical pharmacology/toxicology reviews from the first and second review cycles.

4.2 Labeling

The Nonclinical Pharmacology/Toxicology Reviewer concluded that the proposed draft labeling of Yosprala® conforms to the content and format of labeling for human prescription drug and biological products under 21 CFR 201.57. The Nonclinical Pharmacology/Toxicology Reviewer commented that, however, the revisions below are recommended.

8.1 Pregnancy

The Nonclinical Pharmacology/Toxicology Reviewer commented that the Applicant's proposed version appears to be acceptable. The Nonclinical Pharmacology/Toxicology Reviewer commented that, however, the aspirin data was moved before omeprazole data in order to be consistent with Sections 13.1 and 13.2 of the label. The recommended version is shown below.

Animal Data

Aspirin:
Aspirin produced a spectrum of developmental anomalies when administered to Wistar rats as single, large doses (500-625 mg/kg) on gestational day (GD) 9, 10, or 11. These doses (500 to 625 mg/kg) in rats are about 15 to 19 times the maximum recommended human dose of aspirin (325 mg/day) based on body surface area. Many of the anomalies were related to closure defects and included craniorachischisis, gastroschisis and umbilical hernia, and cleft lip, in addition to diaphragmatic hernia, heart malrotation, and supernumerary ribs and kidneys. In contrast to the rat, aspirin was not developmentally toxic in rabbits.

Omeprazole:
Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at doses up to 69.1 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) during organogenesis did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis) administered during organogenesis produced dose-related increases in embryo- lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis), administered prior to mating through the lactation period.

Esomeprazole:
The data described below was generated from studies using esomeprazole, an enantiomer of omeprazole. The animal to human dose multiples are based on the assumption of equal systemic exposure to esomeprazole in humans following oral administration of either 40 mg esomeprazole or 40 mg omeprazole.

No effects on embryo-fetal development were observed in reproduction studies with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) or in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg esomeprazole or omeprazole on a body surface area basis) administered during organogenesis.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg esomeprazole or omeprazole on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg esomeprazole or omeprazole on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 17 times an oral human dose of 40 mg esomeprazole or omeprazole on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg/kg/day (about 3.4 times an oral human dose of 40 mg esomeprazole or omeprazole on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg esomeprazole or omeprazole on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in the pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg esomeprazole or omeprazole on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg esomeprazole or omeprazole on a body surface area basis).

A pre- and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

8.4 Pediatric Use

The Nonclinical Pharmacology/Toxicology Reviewer commented that the Applicant's proposed version appears to be acceptable. The Nonclinical Pharmacology/Toxicology Reviewer commented that, however, multiples of human exposure values were corrected in appropriate places. The recommended version is shown below.

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 17 to 67 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth *[see Nonclinical Toxicology (13.2)]*.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The Nonclinical Pharmacology/Toxicology Reviewer had the following comments:

- Findings of genotoxicity studies and fertility and reproductive performance studies with omeprazole were duplicated in the Applicant's proposed label.
- Multiples of human exposure values were corrected in appropriate places.
- "No" was added in front of the sentence "astrocytomas were observed in female rats in this study".
- In addition, the following paragraph was not incorporated in the label and was added.

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals *[see Warnings and Precautions (5)]*. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

The recommended version is shown below.

Studies to evaluate the potential effects of YOSPRALA on carcinogenicity, mutagenicity, or impairment of fertility have not been conducted.

Aspirin

Administration of aspirin for 68 weeks at 0.5% in the feed of rats was not carcinogenic.

In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts.

Aspirin inhibits ovulation in rats.

Omeprazole

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.35 to 34 times the human dose of 40 mg per day, based on body surface area) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric

carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 3.4 times the human dose of 40 mg per day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1 to 3.2 times the human dose of 40 mg/day, based on body surface area). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 34 times the human dose of 40 mg per day, based on body surface area). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day (about 34 times the human dose of 40 mg per day, based on body surface area) was found to have no effect on fertility and reproductive performance.

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H2-receptor antagonists.

13.2 Animal Toxicology and/or Pharmacology

The Nonclinical Pharmacology/Toxicology Reviewer commented that the Applicant's proposed version appears to be acceptable. The Nonclinical Pharmacology/Toxicology Reviewer commented that, however, multiples of human exposure values were corrected in appropriate places. The recommended version is shown below.

Aspirin

The acute oral 50% lethal dose in rats is about 1.5 g/kg and in mice 1.1 g/kg. Renal papillary necrosis and decreased urinary concentrating ability occur in rodents chronically administered high doses. Dose-dependent gastric mucosal injury occurs in rats and humans. Mammals may develop aspirin toxicosis associated with GI symptoms, circulatory effects, and central nervous system depression [see *Overdosage (10)*].

Omeprazole

Reproductive Toxicology Studies

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 34 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 3.4 to 34 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138 mg/kg/day (about 3.4 to 34 times the human doses on a body surface area basis).

Juvenile Animal Study

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at oral doses of 70 to 280 mg/kg/day (about 17 to 67 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

4.3 Final Recommendation

An Approval Action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline provided the labeling revisions described above are made.

5. Clinical Pharmacology/Biopharmaceutics

5.1 Issues

The Clinical Pharmacology Reviewer referred to previous clinical pharmacology reviews from the first and second review cycles. The Clinical Pharmacology Reviewer noted that a full clinical pharmacology review was conducted during the first review cycle and the application was acceptable from a clinical pharmacology perspective. The Clinical Pharmacology Reviewer further noted that there was not a new clinical pharmacology study in the second cycle NDA submission.

The Clinical Pharmacology Reviewer summarized the Clinical Pharmacology findings pertinent to the current submission as follows:

> Aspirin Supplier Comparison:
> In this submission, the sponsor changed API aspirin supplier source from (b) (4) to (b) (4) (also referred to as (b) (4)). In addition, aspirin from this new supplier (b) (4)
>
> BA/BE study:
> Aspirin components of PA8140 and PA32540 from the new supplier (b) (4) was bioequivalent to that of previous supplier (b) (4) based on two separate BE studies (PA8140-104 and PA32540-119) that had used partial reference-replicate3-way study design with a reference-scaled average BE approach.
>
> OSI inspection:
> An inspection for bioequivalence (BE) studies PA8140-104 and PA32540-119 for both clinical site and bioanalytical site was requested on 06/21/2016. However, the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection (b) (4) as OSIS recently inspected these sites and the inspectional outcome from the inspections was classified as No Action Indicated (NAI).
>
> Relative BA of omeprazole component of PA8140 vs Prilosec :
> Based on bridged cross-study comparisons, the plasma exposure of IR omeprazole 40 mg from PA8140 was lower than that of Prilosec 40 mg, Prilosec®. Cmax and AUC of IR omeprazole 40 mg from PA8140 were estimated to be 90% and 75%, respectively, of that from an EC formulation omeprazole 40 mg, Prilosec 40 mg following a repeat dose administration for 7 days.

5.2 Recommendation

The Clinical Pharmacology recommendation is the following:

> "The application is acceptable from the clinical pharmacology perspective provided that a mutual agreement is reached on the labeling languages."

The following postmarketing commitment (PMC) is recommended:

> Conduct a clinical PK study evaluating the systemic exposures of the omeprazole degradants that are shown to be present at a higher level at pH <3.0 compared to higher pHs in the in vitro studies (PMC #3111-1). This (b) (4) include both Yosprala and the reference product for the omeprazole component of Yosprala. Compare the individual omeprazole degradant exposures between the two products.
>
> Final Protocol Submission: 11/2017
> Study/Trial Completion: 03/2018
> Final Report Submission: 06/2018

It should be noted that the issue is appropriate for a PMC instead of a pre-approval requirement because prior clinical experience indicates safety and the issue is a theoretical concern. The drug's safety profile has been adequately assessed in the pre-approval program. However, because this product contains non-enteric coated omeprazole, which may be unstable in acidic pH, there is residual uncertainty regarding potential omeprazole degradants in the acidic pH of the stomach. To address this residual uncertainty, a clinical PK study will be conducted to evaluate the systemic exposures of degradants of non-enteric coated omeprazole of Yosprala and degradants of a reference enteric-coated omeprazole product that are shown to be present at higher level at pH <3.0 compared to pHs that exceed 3.0 in the in vitro studies of Yosprala (see PMC #1 template for a discussion of the in vitro studies); the exposures associated with these specific omeprazole degradants will be compared between the two products.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Yosprala is not an antimicrobial agent.

7. Clinical/Statistical - Efficacy

No new clinical efficacy data were submitted in the current submission (third cycle NDA submission) or in the previous submission (second cycle NDA submission). A clinical review was completed in the first review cycle by Zana Marks dated March 21, 2014, and Addenda dated April 4, 2014, and April 16, 2014. The reader is referred to her review and other summary reviews (a CDTL and Division Director review) in which the effectiveness of both doses is extensively discussed.

8. Safety

See the first and second cycle CDTL Reviews for a discussion of the safety findings from the first and second cycle NDA submissions.

In the current resubmission, the applicant submitted an appended document to the Integrated Summary of Safety (ISS) section of the NDA describing the safety findings from two phase 1 BA/BE studies. These studies (PA32540-117 and PA8140-104) were conducted in 72 healthy volunteers (36 subjects in each study); complete safety data from these studies had not been previously submitted to the NDA. See discussion of these studies in Section 5 of this CDTL Review. No other studies with Yosprala Tablets of any strength have been completed in any country.

There are no new safety concerns generated by these two studies and no meaningful conclusions can be drawn given the small number of healthy subjects enrolled. No new changes to the label are warranted based on the results of these small studies.

The applicant states that they have not performed any new safety analyses beyond that which was provided in the NDA "as no new safety information that might affect the analyses submitted in the original ISS have become available."

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

This application triggered PREA as this NDA proposed a new indication for the components of this combination product. The Pediatric Research Committee (PeRC) met during the first review cycle (on September 25, 2013) and agreed to the full waiver on the grounds that studies would be impossible or highly impractical, "because the proposed indication in the pediatric population is rare, therefore the incidence of aspirin associated gastric ulcers would also expected to be rare."

The reader is referred to the first cycle reviews regarding the incorporation into the draft label of data indicating that use of esomeprazole in pregnancy may cause fetal harm with changes in bone morphology and physeal dysplasia in pre- and postnatal developmental toxicity studies in rats (from studies conducted under NDA 202342, esomeprazole strontium).

In the current review cycle, DPMH was consulted for a review of labeling. See the Pediatric Review by Erica Radden, dated August 11, 2016 and the Maternal Health Review by

Christos Mastroyannis, dated August 29, 2016. The DPMH-Pediatric team's current review focused on sections 4 (Contraindications) and 8.4 (Pediatric Use). The DPMH-Maternal Health team's current review focused on recommendations for pregnancy and lactation.

The DPMH Pediatric Review noted that "Based on collaboration with the division, the language describing the contraindication in pediatric patients was modified to provide more clarity regarding the reason for the contraindication similar to the language included in the Contraindications section. Additionally, a heading was included for the juvenile animal data." See below.

4 CONTRAINDICATIONS

YOSPRALA is contraindicated in:

- Pediatric patients with suspected viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

8.4 Pediatric Use

The safety and efficacy of YOSPRALA has not been established in pediatric patients. (b) (4) YOSPRALA is contraindicated in pediatric patients with suspected viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses *[see Contraindications (4)]*.

Juvenile Animal Data

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about (b) (4) 17 to (b) (4) 57 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth *[see Nonclinical Toxicology (13.2)]*.

The DPMH Maternal Health team structured the Pregnancy and Lactation sections of Yosprala labeling to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of Yosprala labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of Yosprala labeling was formatted in the PLLR format to include the "Risk Summary" and "Clinical Considerations" sections.
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" section of Yosprala labeling was formatted in the PLLR format to include the "Infertility" section.
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1, 8.2 and 8.3 of labeling.

8.1 Pregnancy

The sections "Risk Summary," "Clinical Considerations," and "Data" (only the "Human Data" sub-section) are shown below. See Section 4.2 of this CDTL Review for the "Nonclinical" sub-section of the "Data" section.

Risk Summary

Use of NSAIDs, including YOSPRALA, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including YOSPRALA, in pregnant women starting at 30 weeks of gestation (third trimester). There are no available data with YOSPRALA use in pregnant women to inform a drug-associate risk for major birth defects and miscarriage; however, there are published studies with each individual component of YOSPRALA.

Aspirin

Data from controlled and observational studies with aspirin use during pregnancy have not reported a clear association with major birth defects or miscarriage risk. However, NSAIDs, including aspirin, a component of YOSPRALA, may increase the risk of complications during labor or delivery and to the neonate *[see Clinical Considerations and Data]*. In animal reproduction studies, there were adverse developmental effects with oral administration of aspirin to pregnant rats at doses 15 to 19 times the maximum recommended human dose (MRHD) of 325 mg/day. Aspirin did not produce adverse developmental effects in rabbits *[see Data]*.

Omeprazole

Data from epidemiological and observational studies with omeprazole have not reported a clear association with major birth defects or miscarriage risk. Animal reproduction studies in pregnant rats and rabbits resulted in dose-dependent embryo-lethality at omeprazole doses that were approximately 3.4 to 34 times an oral human dose of 40 mg.

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 34 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole *[see Data]*.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Maternal aspirin use during the third trimester of pregnancy may increase the risk of neonatal complications, including necrotizing enterocolitis, patent ductus arteriosus,

intracranial hemorrhage in premature infants, low birth weight, stillbirth and neonatal death.

Maternal Adverse Reactions
An increased incidence of post-term pregnancy and longer duration of pregnancy in women taking aspirin has been reported. Avoid maternal use of aspirin, including Yosprala, in pregnant women during the third trimester.

Labor or Delivery
Aspirin, a component of YOSPRALA, should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. In animal studies, NSAIDS, including aspirin, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data
Human Data
Aspirin
Data from several controlled and observational studies with aspirin use in the first or second trimesters of pregnancy have not reported a clear association with major birth defects or miscarriage risk. Published data on aspirin use during pregnancy has been mostly reported with low dose aspirin (60 to 100 mg). There are limited data regarding aspirin 325 mg or higher doses used during pregnancy.

A prospective, cohort study of 50,282 mother-child pairs (the Collaborative Perinatal Project) assessing adverse outcomes by level of aspirin exposure did not report aspirin-induced teratogenicity, altered neonatal birth weight, or perinatal deaths at any exposure level. In a controlled, randomized trial, maternal risks during pregnancy were reported as low or absent, with no demonstrated increased risk of maternal bleeding or placental abruptio. A multinational study involving more than 9,000 women, CLASP (Collaborative Low-dose Aspirin Study in Pregnancy)], found that low-dose aspirin reduced fetal morbidity in a select population of women with early-onset preeclampsia, but did not identify adverse effects in the pregnant woman, fetus, or newborn (followed to 12 and 18 months of age) in association with the use of low-dose aspirin during pregnancy. In contrast, some case-control studies reported associations between human congenital malformations and aspirin use early in gestation, but these studies did not report a consistent outcome attributable to drug use.

A report from EAGeR trial (Effects of Aspirin in Gestation and Reproduction trial), which evaluated 1078 women who were attempting to become pregnant and had prior miscarriages, reported use of low-dose aspirin without adverse maternal or fetal effects except for vaginal bleeding. Another trial of 3294 pregnant women of 14 to 20 weeks of gestation treated with aspirin showed no effect in the mothers' incidence of pre-eclampsia, hypertension, HELLP syndrome or placental abruptio, or in the incidence of perinatal deaths or low birth weight below the 10th percentile. The incidence of maternal side effects was higher in the aspirin group, principally because of a significantly higher rate of hemorrhage.

Use of NSAIDs, including aspirin, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus and use of high-dose aspirin for long periods in pregnancy may also increase the risk of bleeding in the brain of premature infants.

Omeprazole

Four published epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H_2-receptor antagonists or other controls.

A population-based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995 to 1999, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number of infants exposed in utero to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996 to 2009, reported on 1,800 live births whose mothers used omeprazole during the first trimester of pregnancy and 837,317 live births whose mothers did not use any PPI. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H_2-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H_2-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% with first trimester exposures). The reported rate of major congenital malformations was 4% in the omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease-paired controls. Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

8.2 Lactation

The "Risk Summary" and "Clinical Considerations" sections are shown below.

Risk Summary

There is no information about the presence of YOSPRALA in human milk; however, the individual components of YOSPRALA, aspirin and omeprazole, are present in human milk. Limited data from clinical lactation studies in published literature describe the presence of aspirin in human milk at relative infant doses of 2.5% to 10.8% of the maternal weight-adjusted dosage. Case reports of breastfeeding infants whose mothers were exposed to aspirin during lactation describe adverse reactions, including metabolic acidosis, thrombocytopenia, and hemolysis. There is no information on the effects of aspirin on milk production. Limited data from a case report in published literature describes the presence of omeprazole in human milk at a relative infant dose of 0.9% of the maternal weight-adjusted dosage. There are no reports of adverse effects of omeprazole on the breastfed infant, and no information on the effects of omeprazole on milk production. Because of the potential for serious adverse reactions, including the potential for aspirin to cause metabolic acidosis, thrombocytopenia, hemolysis or Reye's syndrome, advise patients that breastfeeding is not recommended during treatment with YOSPRALA.

Clinical Considerations

It is not known if maternal exposure to aspirin during lactation increases the risk of Reye's syndrome in breastfed infants. The direct use of aspirin in infants and children is associated with Reye's syndrome, even at low plasma levels.

8.3 Females and Males of Reproductive Potential

The "Females and Males of Reproductive Potential" section of Yosprala labeling was formatted in the PLLR format to include the "Infertility" section.

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including YOSPRALA, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also demonstrated a reversible delay in ovulation. Consider withdrawal of NSAIDs, including YOSPRALA, in women who have difficulties conceiving or who are undergoing investigation of infertility.

17 PATIENT COUNSELING INFORMATION

The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1, 8.2 and 8.3 of labeling.

> Fetal Toxicity
> Inform pregnant women to avoid use of YOSPRALA and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closure of the fetal ductus arteriosus *[see Warnings and Precautions (5.18) and Use in Specific Populations (8.1)]*.

11. Other Relevant Regulatory Issues

11.1 Office of Scientific Investigations (OSI) Audits

OSI audits were requested in the first cycle submission of this application. See the CDTL Review by Robert Fiorentino dated April 25, 2014.

11.2 Division of Epidemiology I Review of a Research Article - GI Bleeding from PPI in Patients on Low Dose Aspirin

DEPI I was consulted to review a recently published scientific article about gastrointestinal (GI) bleeding risks from proton pump inhibitors (PPI) in patients on low dose aspirin.[3] See the DEPI I Review by Joel Weissfeld dated July 11, 2016.

The DEPI I Reviewer summarized the review findings as follows:

> A scientific article published by Miyake, et al., 2015, described an excess lower GI bleeding risk from PPI in patients on low-dose aspirin. (b) (4) [redacted]
>
> Miyake used medical records to construct three cohorts of patients (mean age 67.4 years) discharged on low-dose aspirin from a Japanese academic hospital after coronary angiography. After three years follow-up, Miyake documented lower GI bleeding in 9 of 107 (8.4%), 5 of 173 (2.9%), and 4 of 258 (1.6%) patients discharged on PPI, histamine-2 receptor antagonists (H2RA), and neither PPI nor H2RA, respectively. A Cox regression estimated lower GI bleeding risk from PPI use vs. PPI or H2RA nonuse at adjusted hazard ratio 6.55, 95% confidence interval 2.01-12.32.
>
> DEPI found in Miyake serious risk of bias, with major concerns in two domains, confounding control and outcome measurement. Either source for concern could plausibly explain an artificial association in Miyake between PPI and lower GI

[3] Miyake, et al., 2015, Proton Pump Inhibitors are Associated with Lower Gastrointestinal Tract Bleeding in Low-Dose Aspirin Users with Ischaemic Heart Disease, Dig Liver Dis, 47:757-762.

bleeding in patients on low-dose aspirin. Also, DEPI found only weak evidence to support PPI as the causal explanation for the excess lower GI bleeding risk observed by Miyake. Serious risks of bias and weak evidence for causality severely limited the usefulness of results in Miyake.

DEPI recommended that DGIEP not use evidence from Miyake (b) (4)

CDTL Reviewer Comments: ***Based on the concerns with the Miyake study noted above (which "could plausibly explain an artificial association") and the "weak evidence to support PPI as the causal association for the excess lower GI bleeding risk observed", this CDTL Reviewer agrees with the DEPI Reviewer*** (b) (4) ***This CDTL Reviewer*** (b) (4) ***based on the safety findings (see Section 8 of this CDTL Review and previous CDTL Reviews). In addition, the DEPI Reviewer noted the results of a second study:[4] "…a second Japanese case-control study (Nagata, et al., 2015) did not find excess lower GI bleeding risk from intermittent or regular use vs. nonuse in past month of PPI in patients on low-dose aspirin (adjusted odds ratio 1.02, 95% CI 0.62-1.68)". Thus, this CDTL Reviewer does not recommend*** (b) (4)

12. Labeling

The Applicant was requested to revise the physician labeling and patient information. The most notable revisions are summarized below.

12.1 Proprietary Name

For complete information, see the DMEPA Proprietary Name Review by Sherly Abraham, dated May 27, 2016.

DMEPA concluded that the proprietary name of "Yosprala" was acceptable. This was communicated to the Applicant in the Proprietary Name Request Conditionally Acceptable Letter dated May 25, 2016.

12.2 Office of Prescription Drug Promotion (OPDP) Comments

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name (Yosprala) is acceptable from a promotional perspective. This is documented in the Proprietary Name Review by Sherly Abraham, dated May 27, 2016.

[4] Nagata, N, R Niikura, T Aoki, T Sakurai, S Moriyasu, T Shimbo, K Sekine, H Okubo, K Watanabe, C Yokoi, M Yanase, J Akiyama and N Uemura, 2015, Effect of Proton-Pump Inhibitors on the Risk of Lower Gastrointestinal Bleeding Associated with NSAIDs, Aspirin, Clopidogrel, and Warfarin, J Gastroenterol, 50:1079-86.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

Physician Labeling:

As noted in the first cycle CDTL Review, the proposed label was a combined label that incorporated data from omeprazole (Prilosec) and from the aspirin monograph (21 CFR 343.80).

The main revisions to the Applicant's proposed Physician Labeling are summarized below:

- Indications and Usage (Section 1 of Label): The proposed indication statement was revised, but otherwise remained similar to that originally proposed in adherence to the aspirin monograph. A limitation of use section was added to indicate that reduction in risk of GI bleeds due to aspirin has not been demonstrated.

- Dosage and Administration (Section 2 of Label): The following statement was added to the administration instructions:
  "Do not stop taking YOSPRALA suddenly as this could increase the risk of heart attack or stroke."

- Contraindications (Section 4 of Label): The following statement was included (see discussion in Section 10 of this CDTL Review):
  "Pediatric patients with suspected viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses."
  In addition, the following statements were included for consistency with the most recently approved Prilosec label (NDA 22056):
  "YOSPRALA is contraindicated in patients with known hypersensitivity to aspirin, omeprazole, substituted benzimidazoles, or to any of the excipients in the formulation *[see Warnings and Precautions (5.8), Adverse Reactions (6.2)]*."
  "Proton pump inhibitor (PPI)–containing products, including YOSPRALA, are contraindicated in patients receiving rilpivirine-containing products *[see Drug Interactions (7)]."*

- Warnings and Precautions (Section 5 of Label): This section integrated the warnings and precautions for aspirin with those for omeprazole from the most to least significant (see the final labeling for Yosprala). It should be noted that warnings and precautions were included that are consistent with the most recently approved Prilosec label (NDA 22056). In addition, the warning and precaution of cutaneous and systemic lupus erythematosus was included; it should be noted that this warning and precaution is based on new safety information associated with the use of PPIs, and that in accordance with section 505(o)(4) of the FDCA, each of the PPI sponsors was notified that this warning and precaution must be included in their labeling (see Review by Jessica Lee dated June 14, 2015 filed under Tracked Safety Issue 1455). Further, it should be noted that the warning and precaution of Gastrointestinal Adverse Reactions (Section 5.2 of the label) was revised; the wording at the time of this CDTL Review is shown below.

"Aspirin is associated with serious gastrointestinal (GI) adverse reactions, including inflammation, bleeding ulceration and perforation of the upper and lower GI tract. Other adverse reactions with aspirin include stomach pain, heartburn, nausea, and vomiting."

"Serious GI adverse reactions reported in the clinical trials of YOSPRALA were: gastric ulcer hemorrhage in one of the 521 patients treated with YOSPRALA and duodenal ulcer hemorrhage in one of the 524 patients treated with enteric-coated aspirin. In addition, there were two cases of intestinal hemorrhage, one in each treatment group, and one patient treated with YOSPRALA experienced obstruction of the small bowel."

- Adverse Reactions (Section 6 of Label): Safety data from the two clinical trials have been incorporated into this section (see first cycle CDTL Review). It should be noted that the following was included in Section 6.1 (Clinical Studies Experience):

  "*Less Common Adverse Reactions*
  In YOSPRALA-treated patients in the clinical trials there were 2 patients with upper GI bleeding (gastric or duodenal) and 2 patients with lower GI bleeding (hematochezia and large intestinal hemorrhage) and one additional patient experienced obstruction in the small bowel."

- Drug Interactions (Section 7 of Label): A table was included summarizing (by clinical impact and intervention) the following clinically relevant interactions affecting drugs co-administered with Yosprala and interaction with diagnostics: (1) antiretrovirals; (2) heparin and warfarin; (3) methotrexate; (4) CYP2C19 substrates; (5) ticagrelor; (6) digoxin; (7) drugs dependent on gastric pH for absorption; (8) tacrolimus; (9) ACE-inhibitors; (10) beta-blockers; (11) diuretics; (12) NSAIDs; (13) oral hypoglycemics; (14) acetazolamide; (15) uricosuric agents (probenecid); (16) valproic acid; (17) interactions with investigations of neuroendocrine tumors; (18) interactions with secretin simulation test; (19) false positive urine tests for THC; and (20) other ("other drugs metabolized via the cytochrome P450 system (e.g., cyclosporine, disulfiram)). In addition, a second table was included summarizing (by clinical impact and intervention) the following clinically relevant interactions affecting Yosprala when co-administered with other drugs: (1) CYP2C19 or CYP3A4 inducers; and (2) CYP2C19 or CYP3A4 inhibitors.

- Use in Specific Populations (Section 8 of Label):
  - Section 8.1 (Pregnancy) was formatted in the PLLR format to include the "Risk Summary," "Clinical Considerations," and "Data" sections based on the recommendations of the DPMH Maternal Health Team (see Section 10 of this CDTL Review). Note that revisions to the "Nonclinical "sub-section of the "Data" section included recommendations of the Pharmacology/Toxicology Review (see Section 4.2 of this CDTL Review).
  - Section 8.2 (Lactation) was formatted in the PLLR format to include the "Risk Summary" and "Clinical Considerations" sections based on the recommendations of the DPMH Maternal Health Team (see Section 10 of this CDTL Review).
  - Section 8.3 (Females and Males of Reproductive Potential) was formatted in the PLLR format to include the "Infertility" section based on the recommendations of the

DPMH Maternal Health Team (see Section 10 of this CDTL Review).

- Section 8.4 (Pediatric Use) was revised based on the recommendations of the DPMH Pediatric Team (see Section 10 of this CDTL Review). In addition, juvenile animal data were included based on the juvenile animal data with reference to Section 13.2 Nonclinical Toxicology of the label (see discussion in Section 4.2 of this CDTL Review).
- Section 8.5 (Geriatric Use) included a description of the percentage of patients ≥ 65 years of age and ≥ 75 years of age, and the following statement: "No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience with aspirin and omeprazole has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out..."
- Section 8.6 (Renal Impairment) included the following statement about the aspirin component: "Avoid YOSPRALA in patients with severe renal impairment (glomerular filtration rate less than 10 mL/minute) due to the aspirin component."
- Section 8.7 (Hepatic Impairment) included a statement that Yosprala should be avoided in patients with any degree of hepatic impairment and a statement about the aspirin component ("Long-term moderate to high doses of aspirin may result in elevations in serum ALT levels…") and a statement about the omeprazole component ("Systemic exposure to omeprazole is increased in patients with hepatic impairment…").
- Section 8.8 (Asian Population) included the following (related to the omeprazole component): "In studies of healthy subjects, Asians had approximately a four-fold higher exposure to omeprazole than Caucasians. CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. Approximately 15% to 20% of Asians are CYP2C19 poor metabolizers. Tests are available to identify a patient's CYP2C19 genotype. Avoid use in Asian patients with unknown CYP2C19 genotype or those who are known to be poor metabolizers…"

➢ Clinical Studies (Section 14 of Label): Efficacy data from the two clinical trials have been incorporated into this section (see first cycle CDTL Review).

Medication Guide:

The following information (under the heading "**What is the most important information I should know about YOSPRALA?**") was revised as shown to reflect the revisions to Section 5.2 of Physician Labeling.

YOSPRALA may help reduce the risk of stomach ulcers from aspirin use, but you could still have bleeding and stomach or intestine ulcers, or other serious stomach or intestine problems. Talk with your doctor.

Carton and Container Labeling:

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the carton and container labels. They made a number of recommendations that were communicated to the Applicant on August 17, 2016 (see DMEPA Label and Labeling Review).

1. As currently presented, the proprietary name is difficult to read [redacted]. We recommend that you increase the prominence of the proprietary name to improve readability.

2. We recommend that you include a space between the numerical strength and unit of measure (e.g. 81 mg/40 mg vs. 81mg/40mg) as the letter "m" can be confused for a zero or two zeros.

3. Consider combining the two dosage statements on the left and right of the principal display panel to the following statement: "Usual dose: Take 1 tablet daily at least 60 minutes before a meal. Tablet should be swallowed whole with liquid."

On August 26, 2016, the Applicant submitted a response stating that they have accepted all the changes above.

In addition to these revisions, additional revisions were negotiated with the Applicant.

Many of the revisions made are based on recommendations from the DMEPA Label and Labeling Review, the OPDP Label Review, the DMPP Patient Labeling Review, and the DPMH Reviews. The reader is referred to each of these reviews for complete information.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The recommended regulatory action is Approval as the CR Item from the previous review cycle has been addressed. Deficiencies identified in the inspection of the [redacted] facility were the basis of the previous CR action (see Section 2.1.2 of this CDTL Review). In this submission, the sponsor changed API aspirin supplier source from [redacted] to [redacted] (also referred to as [redacted]); the Clinical Pharmacology Reviewer concluded that Aspirin components of PA8140 and PA32540 from the new supplier [redacted] was bioequivalent to that of previous supplier [redacted] (see Section 5 of this CDTL Review). The Office of Facility and Process has made a final overall manufacturing Inspection 'Approve' recommendation for the facilities involved in this application (see Section 3.2.7 of this CDTL Review).

13.2 Risk Benefit Assessment

The Risk Benefit Assessment has not changed since the first cycle CDTL review. Refer to the CDTL review dated 04/25/2014.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No special postmarketing risk management activities are recommended for this Application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

No postmarketing required pediatric studies are recommended.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

None of the primary review disciplines had recommendations for additional postmarketing requirements.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The following postmarketing commitments (PMCs) are recommended for the current application, with the following language for the Approval Letter. .

3111-1 Conduct an in vitro study to characterize and quantify the degradants of immediate release omeprazole of Yosprala at various pHs (i.e., pH 1, 1.5, 2, 2.5, 3, 3.5, 4) following a minimum of 1 hour of exposure at 37°C, and evaluate the differences in the profiles across pHs. Submit the chromatograms and a summary of quantitative data generated during the study.

Final Protocol Submission:	01/2017
Study/Trial Completion:	04/2017
Final Report Submission:	06/2017

3111-2 Conduct a clinical PK study evaluating the systemic exposures of the omeprazole degradants that are shown to be present at a higher level at pH <3.0 compared to higher pHs in the in vitro studies (PMC #3111-1). This (b) (4) include both Yosprala and the reference product for the omeprazole component of Yosprala. Compare the individual omeprazole degradant exposures between the two products.

Final Protocol Submission:	11/2017
Study/Trial Completion:	03/2018
Final Report Submission:	06/2018

13.7 Recommended Comments to Applicant

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANIL K RAJPAL
09/14/2016