

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205103Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Donna J. Griebel, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA#</b>	205103
<b>Applicant Name</b>	Aralez Pharmaceuticals
<b>Date of Submission</b>	March 14, 2016
<b>PDUFA Goal Date</b>	September 14, 2016
<b>Proprietary Name / Established (USAN) Name</b>	Yosprala/ aspirin/omeprazole
<b>Dosage Forms / Strength</b>	Tablet/ aspirin: 81 mg or 325 mg omeprazole 40 mg
<b>Proposed Indication(s)</b>	<p>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.</p> <p>The aspirin component of YOSPRALA is indicated for:</p> <ul style="list-style-type: none"> <li>• 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,</li> <li>• reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris,</li> <li>• reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris,</li> <li>• 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.</li> </ul> <p>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 (<math>\geq 55</math>) or documented history of gastric</p>

	ulcers.
<b>Action:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Cycle 1: Zana Marks, MD
Statistical Review	Cycle 1: Milton C. Fan, PhD/Freda Cooner, PhD
Pharmacology Toxicology Review	Tamal Chakraborti, PhD/Sushanta Chakder, PhD
OPQ Review	Current Cycle: See table below
Clinical Pharmacology Review	Dilara Jappar, PhD/Sue-Chih Lee, PhD
DPMH	Erica Radden, MD/Donna Snyder, MD/John Alexander, MD, MPH Christos Mastroyannis, MD/Tamara Johnson, MD, MS/Lynne Yao, MD
OPDP	Meeta Patel, PharmD
OSIS	Shila Nkah/ Hasan Irier, PhD/Young Moon Choi, PhD
CDTL Review	Current Cycle: Anil Rajpal, MD Cycles 1 and 2: Robert Fiorentino, MD
OSE/DMEPA	Sherly Abraham, RPH/Mishale Mistry, PharmD
OSE/DEPI I	Joel L. Weissfeld, MD, MPH/Simone P. Pinheiro, ScD MSc
DMPP	Karen Dowdy, RN, BSN/LaShawn Griffiths, MSHS-PH, BSN, RN

OND=Office of New Drugs  
 OPDP=Division of Drug Marketing, Advertising and Communication  
 DPMH=Division of Pediatric and Maternal Health  
 OPQ=Office of Pharmaceutical Quality  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DEPI=Division of Epidemiology I  
 OSIS=Office of Study Integrity and Surveillance  
 DMPP=Division of Medical Policy Programs  
 CDTL=Cross-Discipline Team Leader

<b>Quality Review</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Xavier Ysem, Ph.D.	OMPT/CDER/OPQ/ONDP/D ND API/NDBII
Drug Product	Zhengfang Ge, Ph.D.	OMPT/CDER/OPQ/ONDP/D ND PII/BV
Process	Jingbo Xiao, Ph.D.	OMPT/CDER/OPQ/OPF/DIA/ IA/BII
Microbiology	Jingbo Xiao, Ph.D.	OMPT/CDER/OPQ/OPF/DIA/ IA/BII
Facility	Christina Capacci-Daniel, Ph.D.	OMPT/CDER/OPQ/OPF/DIA/ IA/BII

<b>Quality Review</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Biopharmaceutics	Hansong Chen, Ph.D.	<b>CDER/OPQ/ONDP/DB II</b>
Regulatory Business Process Manager	Truong Quach, Phar. D.	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Application Technical Lead	Danuta Gromek-Woods, Ph.D.	OMPT/CDER/OPQ/ONDP/D NDPII/BV
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue Jr.	OGROP/ORA/OO/OMPTO/D MPTPO/MDTP
Environmental Analysis (EA)	NA	NA

## Division Director Review

### 1. Introduction

This is the third review cycle for this 505(b)(2) NDA for a fixed combination product (aspirin and omeprazole). The application was considered approvable by all review disciplines at the completion of the first review cycle, with the exception of the CMC reviewers due to a Withhold recommendation from the Office of Compliance. Deficiencies were found during the inspection of the (b)(4) Manufacturing facility, which supplied the aspirin drug substance for the product. The first CR letter was issued on April 25, 2014. A second CR letter was issued on December 16, 2014 due to continued facility deficiencies (b)(4)

In this resubmission, the applicant proposes a new supplier for the aspirin drug substance (b)(4). The change in drug substance supplier for the aspirin component of this fixed combination product necessitated submission and review of new biopharmaceutical data and two relative BA/BE studies comparing the PK of the aspirin components of the two aspirin dose levels of the combination products produced in the original (b)(4) facility and the new (b)(4) facility.

### 2. Background

See Introduction above and the detailed regulatory history outlined in the CDTL review. See also my two previous Division Director reviews for this NDA. The major review issue identified this cycle related to the Biopharmaceutics reviewers' concerns regarding the loss of omeprazole when the product was exposed to acid in *in vitro* dissolution studies. See Section 3 for details regarding this issue.

The original applicant was Pozen, Inc. The applicant for the current resubmission is Aralez Pharmaceuticals, Inc. The latter was formed by a merger between Pozen, Inc. and Tribute Pharmaceuticals Canada, Inc.

### 3. CMC

I concur with the OPQ review team's conclusions and recommendation for approval. They have determined that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product. The Office of Facility and Process has made a final overall "Approve" recommendation based on the inspection of manufacturing facilities. OPQ recommends approval with an expiration dating period of 36 months.

This fixed combination drug product consists of an aspirin core, which is surrounded by coating, a layer of omeprazole, and external film coats. The product contains (b) (4) film coats. The schematic of the product, reproduced from the OPQ review, is shown below.

**Figure 1: Schematic of Yosprala**



As described in Section 1 above, manufacturing facility issues at the (b) (4) site, which produced the aspirin drug substance, led to issuance of two CR letters. In this submission the applicant withdrew the site (b) (4) and replaced it (b) (4). See Section 5 Clinical Pharmacology for a description of the BA studies performed to demonstrate bioequivalence of the products manufactured with aspirin drug substance from the new site vs. the drug product manufactured with aspirin drug substance from the original site.

Although the Biopharmaceutics reviewers have recommended approval, they raised concerns regarding the degradation of omeprazole in the acidic medium of the stomach, based on the results of the in vitro tablet dissolution test results presented in the application. They stated:

*“The dissolution of Yosprala tablet in acid medium (0.1 N HCl) demonstrated that (b) (4) [redacted]”*

The following figure summarizes these data.

**Figure 2:**



The Biopharmaceutics reviewers presented their concerns about these data to the overall review team, and entered an addendum review stating that they deferred to the nonclinical and clinical reviewers to assess the *in vivo* safety of the degradants that would be expected to be formed when Yosprala is exposed to stomach acid. The OPQ, Clinical, Clinical Pharmacology and Pharm/Tox reviewers met in multiple team meetings to discuss the safety issues raised by the Biopharmaceutics reviewers.

The Clinical and Clinical Pharmacology reviewers noted that the loss of omeprazole in stomach acid does not raise efficacy issues because the clinical trials have established the efficacy of the product. Regarding safety issues raised by degradation of omeprazole by stomach acid, the OPQ and Pharm/Tox reviewers noted that the actual omeprazole acid degradation products formed by exposure of Yosprala are unknown. The OPQ reviewers cited a publication from Lindberg, et al<sup>1</sup> that included a list of a number of degradant products, with structures, that may be formed when omeprazole is exposed to acidic conditions. The team could not find data in the literature characterizing the safety of these specific molecules. The PharmTox reviewers, including the Associate Director of Pharmacology/Toxicology, Abby Jacobs, PhD, strongly stated that the molecular products of omeprazole that result from stomach acid exposure are “metabolites, not degradants” as the exposure to acid occurs within the human body, and they stated ICH Q3(B) applies to this situation. They specifically referred to the following in ICH Q3(B):

“Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the levels specified. The applicant should provide a rationale for establishing degradation product acceptance criteria that includes safety considerations. The level of any degradation product present in a new drug product that has been adequately tested in safety **and/or clinical studies would be considered qualified**. [emphasis added] Therefore, it is useful to include any available information on the actual content of

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<sup>11</sup> Lindberg P, Brandstrom A, et al. Medicinal Research Reviews, Vol 10, No. 1, 1-54 (1990)

degradation products in the relevant batches at the time of use in safety and/or clinical studies. **Degradation products that are also significant metabolites present in animal and/or human studies are generally considered qualified** [emphasis added]”.

Yosprala has been investigated in two large phase 3 trials and no unusual safety signal was identified in the clinical review of those trials during the initial review cycle. The CDTL for the current review cycle, Dr. Rajpal, MD, reassessed the Clinical Safety review written by Dr. Zana Marks, MD in the first review cycle, and reported that even when viewed from the vantage point of this new safety question raised by the Biopharmaceutics reviewers, he identified no new safety signal. Furthermore, he evaluated the safety data submitted from the BA/BE trials submitted in the current resubmission, and found no safety signal in those data.

The Pharmacology/Toxicology reviewers noted that the applicant had conducted a rat PK study comparing (b)(4) omeprazole, which revealed a qualitatively similar metabolite profile (plasma and urine) (b)(4). However, they pointed out that rodent stomach pH is somewhat higher than human stomach pH, i.e., approximately 3.2 to 3.9, as compared to 1.5 to 3.5 in humans.

The publications by Lindberg, et al<sup>2</sup> and by Shin and Kim<sup>3</sup> summarize the physiology of the parietal cell and the mechanism of action of proton pump inhibitors in parietal cells. In the resting state, the parietal cell contains cytoplasmic tubulovesicles that fuse to form a secretory canaliculus when the cell is stimulated. The H<sup>+</sup>, K<sup>+</sup>-ATPase (proton pump) is localized in the lining of the secretory canaliculus. H<sup>+</sup> and Cl<sup>-</sup> ions are transported into the canaliculus to the stomach lumen, in exchange for entry of K<sup>+</sup> into the parietal cell's cytosol. The environment in the canaliculus is an acidic environment, i.e., pH of ≤1. Intravenously administered <sup>3</sup>H-labeled omeprazole has been shown in animal studies to localize to the gastric mucosa, and microscopy reveals that the drug localized specifically within parietal cells. Electron microscopy has revealed that the omeprazole localizes within the tubulovesicles and the secretory canalicular membranes. Omeprazole, a weak base (pKa=4), remains in its base form at physiological pH; however, when it diffuses into the secretory canaliculus of the parietal cell, the molecule becomes exposed to a very low pH and undergoes protonation, which traps it in the acid compartment of the parietal cell. It undergoes further acid conversion to the sulfonamide structure which is the inhibitor of the proton pump. Lindberg, et al. describe other molecular changes that occur in the presence of acid. Therefore, acid degradation is occurring even with coated/acid-protected omeprazole products, after systemic absorption. In fact, omeprazole is a prodrug that requires acid conversion to the molecular structure that will interact with the proton pump. Presumably, additional molecular products of acid degradation of omeprazole are forming in the canaliculus, and some of those degradants may be reabsorbed, as the canaliculus opens to the stomach lumen, and the degradants could potentially pass into stomach contents. The reviewers identified no data in the literature that describe measurement of systemic exposure to various potential omeprazole acid degradation products.

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<sup>2</sup> Lindberg P, Brandstrom A, et al. Medicinal Research Reviews, Vol 10, No. 1, 1-54 (1990)

<sup>3</sup> Shin JM and Kim N. J Neurogastroenterol Motil, Vol 19, No. 1, 25-35 (January 2013)

I concur with Dr. Rajpal's summary of the review team's conclusions regarding this issue. The clinical trials revealed no new safety issues potentially attributable to the acid degradation of the omeprazole in Yosprala. The acid degradant issues were thoroughly explored by the review team and do not change the risk/benefit assessment of Yosprala from the conclusions of the previous review cycles. I concur with the team's recommendation for PMCs to further explore the issue. Two investigations will be included in the Approval letter as PMCs:

3111-1 Conduct an in vitro study to characterize and quantify the degradants of the 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. 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 trial 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 trial will 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

The pH range selected for the in vitro study to assure that testing is conducted over a range that covers the pH of the rat stomach and humans.

## 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the Pharmacology/Toxicology reviewer that there are no outstanding Pharm/Tox issues that preclude approval. No new nonclinical toxicology data were submitted in this resubmission. The Pharmacology/Toxicology reviewers worked with the DPMH reviewers to assure that the product label conforms to the Pregnancy and Lactation Labeling Rule (PLLR). See the description in Section 3 of the Pharm/Tox reviewers' contributions to discussions regarding omeprazole acid degradation products.

## 5. Clinical Pharmacology

I concur with the conclusions reached by the Clinical Pharmacology reviewer that there are no outstanding Clinical Pharmacology issues that preclude approval. As stated in Section 1 Background of my review, in response to the last CR letter, the applicant now proposes to

change to a new supplier of the aspirin drug substance for Yosprala. They have changed from (b) (4) to (b) (4) (referred to here as (b) (4)). The drug substances (b) (4) summarized in the table below reproduced from the Clinical Pharmacology Review. (b) (4)

**Table 1: Comparison of ASA (b) (4) Sourced From (b) (4) (Current Source) and (b) (4) (New Source)**

(b) (4)	(b) (4)
(b) (4)	(b) (4)

The applicant submitted the results of two separate BE studies (Study PA8140-104 and Study PA32540-119) to bridge the Yosprala drug products manufactured with aspirin drug substance made at these two different facilities. One study, PA8140-104 compared the acetylsalicylic acid concentrations between Yosprala (81 mg aspirin/40 mg omeprazole) manufactured from aspirin supplied from the (b) (4) site vs the (b) (4) site. The other study, PA32540-119, compared the acetylsalicylic acid concentrations between Yosprala (325 mg aspirin/40 mg omeprazole) manufactured from aspirin supplied from the (b) (4) site vs the (b) (4) site. The Clinical Pharmacology reviewer concluded that the aspirin components from the two suppliers were bioequivalent for both Yosprala dose levels.

The Office of Study Integrity and Surveillance (OSIS) inspected the bioanalytical portions of Studies PA8140-104 and PA32540-119. OSIS recommended accepting the analytical data from both studies for review. The reviewers from OSIS Division of New Drug Bioequivalence Evaluation recommended accepting data from the clinical site that conducted the BE trials without on-site inspection because the inspectional outcome from a recent inspection of the site was No Action Indicated (NAI).

The Clinical Pharmacology reviewer also addressed the relative bioavailability of omeprazole in the Yosprala (81 mg aspirin/40 mg omeprazole) product vs. the Prilosec 40 mg reference product in this review cycle. Given the available clinical guidelines for aspirin as secondary prevention, we anticipate that if Yosprala is prescribed, it is most likely that the lower aspirin dose combination will be selected. The reviewers had previously evaluated data comparing the omeprazole exposure associated with the Yosprala (325 mg aspirin/omeprazole 40 mg) dose level to the Prilosec 40 mg reference product on days 1, 5 and 7 (Study PA32540-112). The Day 1 PK had also been compared in Study PA32540-113. The reviewers also previously evaluated comparative omeprazole PK data between the two aspirin dose levels of Yosprala (325 mg/40 mg vs. 81 mg/40 mg) on Day 7 only in Study PA8140-103 (no direct comparison to the reference Prilosec product occurred in this study). During this review cycle the Clinical Pharmacology reviewer summarized the Day 7 omeprazole PK data for the two Yosprala dose levels and Prilosec 40 mg from the previously reviewed studies, which are shown in the table below (reproduced from her review).

**Table 2: Cross-study Comparison of Omeprazole Exposure from PA8140, PA32540 and Prilosec 40 mg on Day 7**

Treatment	Statistics	Cmax (ng/mL)	AUC0-24 (hr*ng/mL)	Source (study #)
PA8140	N	30	30	PA8140-103
	Mean	1488	3063	
	%CV	71	101	
	GeoMean	1094	1920	
PA32540	N	30	30	PA8140-103
	Mean	1385	2288	
	%CV	73	91	
	GeoMean	1051	1513	
PA32540	n	26	26	PA32540-112
	Mean	1196	2187	
	%CV	71	88	
	GeoMean	903	1446	
Prilosec 40 mg + Ecotrin 325 mg	n	26	26	PA32540-112
	Mean	1345	2985	
	%CV	44	59	
	GeoMean	1218	2558	

Upon request during this review cycle, the applicant provided the Day 7 (after once daily dosing x 7) geometric mean ratio and associated confidence interval for CMax and AUC comparisons for omeprazole between the Yosprala (81mg aspirin/40 mg omeprazole) dose level and the reference product, Prilosec 40 mg. The data utilized in this cross study analysis came from Study PA32540-112 (Prilosec 40 mg Day 7 data) and Study PA8140-103 (Yosprala 81 mg aspirin/omeprazole 40 mg Day 7 data). The Clinical Pharmacology reviewer concluded that the data from these cross study comparisons were reasonable given that they were generated by the same sponsor with similar bioanalytical methodology at the same bioanalytical site with one common treatment present in both studies (bridged cross study comparison). The Statistical reviewer evaluated the applicant's statistical methodology for calculation of the geometric mean ratio and confidence intervals and concluded the approach was reasonable. The results are summarized in the table below (reproduced from the Clinical Pharmacology review). The upper bounds for the 90% confidence intervals did not exceed 125%. The lower bounds fell below 80%; however, this does not raise an efficacy concern given that the Yosprala 325 mg aspirin/40 mg omeprazole product was found effective in clinical trials, and the omeprazole exposures associated with the two Yosprala dose levels were similar when compared head to head in Study PA8140-103.

**Table 3: Geometric Mean Ratios and 90% Confidence Intervals for  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-24}$  of Omeprazole from PA8140 to Prilosec® on Day 7 based on Bridged Cross-Study Comparisons**

Parameter	PA8140 <sup>1</sup> vs Prilosec 40 mg <sup>2</sup> on Day 7 GLSM Ratio % (90% Confidence Interval)
$C_{max}$ (ng/mL)	89.76 (64.79-124.36)
$AUC_{0-t}$ (hr*ng/mL)	74.97 (50.92-110.36)
$AUC_{0-24}$ (hr*ng/mL)	75.05 (51.00-110.44)

GLSM = geometric least-squares mean.

1: PA8140 is from study PA8140-103 Treatment A: One tablet of PA8140 (delayed-release aspirin 81 mg and immediate release omeprazole 40 mg) administered once daily for 7 consecutive days.

2: Prilosec 40 mg is from study PA32540-112 Treatment B: One tablet of EC-ASA (Ecotrin®) 325 mg and one capsule EC omeprazole (Prilosec®) 40 mg administered once daily for 7 consecutive days.

Refer to the original Clinical Pharmacology review and my first cycle Division Director review for details regarding the omeprazole BA/BE PK studies initially submitted with the NDA. In the previously reviewed head to head comparison of the two Yosprala dose levels, Study PA8140-103, the Day 7 omeprazole GLSM ratio with 90% CI for 81mg/40mg vs. 325 mg/40 mg for  $C_{max}$  was 1.04 (0.86-1.27); for  $AUC_{0-t}$  it was 1.27 (1.04,1.54). Study PA32540-112, which compared Yosprala 325mg/40mg (the product evaluated in the efficacy trials) vs. Prilosec 40 mg revealed that Day 7 omeprazole exposures for Yosprala were relatively low compared to Prilosec: Day 7  $C_{max}$  = 0.74 (0.59-0.93) and  $AUC_{0-24}$  = 0.57 (0.45-0.73).

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical-Efficacy

There were no new efficacy data submitted for review in this review cycle. See previous reviews for discussion of the phase 3 trials conducted to establish the efficacy of the omeprazole component of Yosprala for reducing the risk of developing aspirin associated gastric ulcers.

## 8. Safety

See the first cycle CDTL Review for a discussion of the safety findings from the first cycle NDA submissions. In the current submission, the applicant submitted the summary safety data from the two BA/BE studies conducted in a total of 72 healthy subjects to support change in the manufacturing site. The CDTL evaluated those data and identified no new concerns.

DEPI I was consulted to review a publication by Miyake, et al, 2015, which described an excess of lower GI bleeding risk from concomitant use of PPIs with low-dose aspirin. Lower GI bleeding has been reported as an adverse reaction associated with aspirin. The publication suggested that concomitant PPI use with aspirin may further increase that risk. The review team questioned whether this publication should be (b) (4)

The DEPI reviewer evaluated the publication and found evidence of serious risk of bias. He stated that confounding control and/or outcome measurement could result in an artificial association between PPI and lower GI bleeding. Furthermore, he identified another publication by Nagat, et al, 2015, that did not find an excess risk of lower GI bleeding in patients taking PPIs with low-dose aspirin. He concluded that the currently available evidence (b) (4) The CDTL and I concurred with this recommendation.

The Yosprala label was evaluated this cycle to assure that any class labeling relevant to PPIs had been included in the product label. Warnings and Precautions were included to be consistent with the most recently approved Prilosec label (NDA 22056), including a Warning and Precaution for acute interstitial nephritis. A new class Warning and Precaution of cutaneous and systemic lupus erythematosus was also included. The reviewers further revised the Warning and Precaution for Gastrointestinal Adverse Reactions during this review cycle to add the description of serious GI adverse reactions reported in the Yosprala clinical trials, as follows (newly added wording presented here in italics):

“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.”*

In addition, further modifications of Section 6 Adverse Reactions of the label resulted in the addition of the following statement:

*“Less Common Adverse Reactions*

*In YOSPRALA-treated patients in the clinical trials there were 2 patients with 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.”*

Given that Yosprala is a fixed combination and does not allow reducing the omeprazole dose in the setting of a patient who is a CYP2C19 poor metabolizer, Section 8.8 of the label was added during this review cycle to state that the product should be avoided in Asian patients with unknown CYP2C19 genotype or those who are known to be poor metabolizers. The updated label will state:

“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...”

## **9. Advisory Committee Meeting**

There was no advisory committee meeting to discuss this application.

## **10. Pediatrics**

See my previous reviews. PREA will be waived because 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."

In the current review cycle, the DPMH reviews recommended labeling revisions to assure that the label complied with PLLR. Those revisions were incorporated. In addition, DPMH recommended modification of the wording in Section 8.4 to provide consistency with the Contraindication for pediatric use in Section 4 of the product label. Section 17 Patient Counseling Information was also updated to correspond to the changes in Sections 8.1, 8.2 and 8.3 related to PLLR.

## **11. Other Relevant Regulatory Issues**

See previous reviews from earlier review cycles for information on DSI audits and financial disclosures.

## **12. Labeling**

DMEPA and OPDP concluded that the proprietary name “Yosprala” was acceptable during this review cycle.

See Sections 8 and 10 above and previous reviews from earlier cycles for additional labeling review issues. In addition, during this cycle, Section 7 Drug Interactions of the product label was revised to present the information in tabular format.

See the CDTL review for a more detailed and comprehensive description of the labeling revisions that occurred during this review cycle.

### **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action - Approval

- Risk Benefit Assessment

As stated in my Risk Benefit Assessment from the initial review cycle, “Both components of this fixed combination are approved drugs and the applicant presented substantial evidence that the omeprazole component of the fixed combination reduces the risk for gastric ulcers induced by enteric coated aspirin 325 mg. The applicant also established bioequivalence based on the active moiety of ASA, i.e., acetylsalicylic acid, for both combination presentations (ASA 325 mg/omeprazole 40 mg; ASA 81 mg/omeprazole 40 mg). Based on the monograph for aspirin professional labeling (21 CFR 343.80), the secondary cardiovascular prevention indications can be included in the Yosprala label.

Although no adequate and well controlled trials that evaluated the efficacy of the ASA 81mg + IR omeprazole 40mg Yosprala tablet (PA8140) were submitted for review, I concur with the CDTL that there is adequate evidence to support the approval of the lower ASA dose combination, since there is no reason to believe that ASA 81 mg would have a greater risk for development of gastric ulcers, making it more difficult for the omeprazole to reduce the risk of ulcers, and given that there is evidence in the literature indicating that there is in fact a risk for developing upper gastrointestinal injury, including ulcers, with aspirin doses lower than 325 mg. Furthermore, PK data from a relative bioavailability study (Study PA 8140-103) established that the bioavailability of the omeprazole component of the lower ASA dose fixed combination product (81/40) was not lower than that of the fixed combination tested in the two phase 3 trials (325/40).

The DCRP concerns regarding marketing a combination that includes a 325 mg dose of aspirin when lower doses of aspirin have been found to be effective for secondary prevention were carefully considered, including the concerns about increasing risk for bleeding with increasing doses of aspirin. These issues were discussed with OND and CDER leadership, and in light of inclusion of the ASA 325 mg dose in 21 CFR343.80, a decision to limit approval to the 81 mg ASA combination was not supported. Presumably, when practice of medicine aligns with clinical guidelines for secondary prevention, based on comparable efficacy and apparent improved safety for lower ASA doses, the lower dose combination product presentation will be selected for use by clinicians. The review team has worked to assure that Yosprala labeling will address DCRP concerns. The Dosage and Administration section will encourage prescribers to consider current practice guidelines and the potential for an increased risk of bleeding with increasing aspirin doses when selecting the Yosprala aspirin dose. A Limitation

of Use in the indication will state that the omeprazole component has not been shown to reduce the risk of upper GI bleeding. In fact, upper gastrointestinal hemorrhage occurred in the trials submitted for review (an SAE in each treatment arm). An additional Limitation of Use statement will inform prescribers that Yosprala is not appropriate for use in an acute cardiovascular event setting due to the delayed release characteristics of the aspirin component.

Safety labeling associated with currently approved omeprazole and NSAID products will be included in the Yosprala product label. These have been discussed in my review and include new animal safety data and pregnancy warnings for Prilosec, as well as an interaction with clopidogrel.”

During this review cycle, the applicant has provided BA/BE studies to establish that the manufacturing change for the aspirin drug substance does not impact our previous conclusion regarding the safety and efficacy of the aspirin component of Yosprala. The risk/benefit conclusion from the original submission has also not changed for the overall fixed combination product. The label was updated to include new class labeling for the omeprazole PPI component of Yosprala in the Warnings and Precautions section. These new class Warnings do not change my Risk Benefit conclusions that benefits of the product outweigh the risks. A Limitation of Use in the indication section of the label was included in the previous review cycle to make it clear that the clinical trials had not demonstrated an actual reduction in the risk of upper GI bleeding. The label was further strengthened in this review cycle to add additional information on the GI bleeding observed in the Yosprala arms of the clinical trials (which had previously only been presented in Section 14 Clinical Studies) to the previous GI Adverse Reactions Warning and Precaution and to Section 6.1 Adverse Reactions.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None.
- Recommendation for other Postmarketing Requirements and Commitments

See Section 3 and the Approval letter for the two PMCs. PREA was waived. (See Section 10.)

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/s/  
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DONNA J GRIEBEL  
09/14/2016