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APPLICATION NUMBER:

205103Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205103	Submission Date(s): 03/14/2016, 5/2/2016, 7/20/2016
Submission Type; Code	Resubmission
Brand Name	Yosprala
Generic Name	Aspirin Delayed Release/Omeprazole Immediate Release
Reviewer	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	POZEN, Inc
Formulation; Strength(s)	Tablet, 81 mg or 325 mg Aspirin/40 mg Omeprazole
Proposed Indication	Use in the secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Proposed Dosing Regimen	Once Daily tablet
PDUFA Goal Date:	09/14/2016

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1 Executive Summary

This is a 505(b)(2) application for Yosprala (Delayed Release Aspirin/Immediate Release omeprazole) tablets referencing Ecotrin® (EC-Aspirin) and Prilosec® (EC-Omeprazole). The proposed product is an oral fixed dose combination product containing 81 mg or 325 mg aspirin in the inner enteric coated core (delayed release) surrounded by 40 mg omeprazole in the immediate-release film coat to release the active ingredients in a sequential fashion.

The original application was submitted on 03/25/2013. A full clinical pharmacology review was conducted during the 1st review cycle and application was acceptable from clinical pharmacology perspective. Please see Clinical Pharmacology review dated 04/18/2014. However, this application was issued a Complete Response (CR) action letter on 04/25/2014 due to facility inspection deficiencies at (b) (4) manufacturing facility, which was a supplier to aspirin drug substance used to manufacture Yosprala tablets. There were no deficiencies from clinical pharmacology perspective.

The sponsor submitted a response to the Complete Response action letter (resubmission) on June 30, 2014. There was no new clinical pharmacology study in that submission. Please see clinical pharmacology review dated 11/24/2014. That submission was issued another Complete Response (CR) action letter on 12/16/2014 due to facility inspection deficiencies at aspirin substance supplier (b) (4) manufacturing facility again.

In this 3rd submission, the sponsor submitted another response to Complete Response action letter (resubmission) on March 14, 2016. In this submission, in order to address its manufacturing facility deficiency, the sponsor had changed the supplier for aspirin (b) (4) component from the previous supplier (b) (4) to a new supplier (b) (4) (also referred to as (b) (4)) (b) (4) The omeprazole for Yosprala Tablets and the manufacturing process for Yosprala Tablets remain completely unchanged. To support these changes in aspirin supplier, in addition to in-vitro testing, the sponsor submitted two relative BA/BE study comparing the aspirin components of PA32540 and PA8140 (b) (4) (b) (4)

1.1 Recommendation

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

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

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 [redacted]

BA/BE study:
Aspirin components of PA8140 and PA32540 from the new supplier [redacted] was bioequivalent to that of previous supplier [redacted] 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 [redacted] 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.

2 Question Based Review

2.1 What are the differences in aspirin API from the two suppliers?

In this submission, the sponsor changed API aspirin supplier source from [redacted] to [redacted] (also referred to as [redacted]). In addition, aspirin from this new supplier [redacted]

Table 1: Comparison of ASA [redacted] Sourced From [redacted] (Current Source) and [redacted] (New Source)

[redacted]

Table 2: Comparison of PA8140 Aspirin Core Tablet Formulation [redacted]

Components	Quantity per unit (mg/tablet)	

Table 3: Comparison of PA32540 Aspirin Core Tablet Formulation (b) (4)

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