CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205103Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	205103
Supporting document/s:	046
Applicant's letter date:	March 14, 2016
CDER stamp date:	March 14, 2016
Product:	PA8140 and PA32540 (Yosprala®, Aspirin/Omeprazole) Tablets
Indication:	For use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Applicant:	POZEN, Inc.
Review Division:	DGIEP
Reviewer:	Tamal Chakraborti, PhD
Supervisor:	Sushanta Chakder, PhD
Division Director:	Donna Griebel, MD
Project Manager:	Brian Strongin, RPh, MBA

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3

INTRODUCTION 3
BRIEF DISCUSSION OF NONCLINICAL FINDINGS 3
RECOMMENDATIONS 3

STUDIES SUBMITTED 3

STUDIES REVIEWED 3
STUDIES NOT REVIEWED 4
PREVIOUS REVIEWS REFERENCED 4

INTEGRATED SUMMARY AND EVALUATION 13

Executive Summary

Introduction

Yosprala (Aspirin/Omeprazole) delayed-release tablets, 81 mg/40 mg (PA 8140) and 325 mg/40 mg (PA 32540) was originally submitted on March 25, 2013, as a 505(b)(2) application indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers. On April 25, 2014, a Complete Response (CR) letter was issued. The CR deficiencies included the following items: 1) Manufacturing facility inspection deficiencies and 2) Labeling deficiencies. On June 30, 2014, the Applicant submitted a resubmission (SDN 036) responding to the above CR letter. On December 16, 2014, a second CR letter was issued as the manufacturing facility deficiencies were not fully resolved along with the other deficiencies, which included the following:

1. Manufacturing facility inspection deficiencies
2. Labeling deficiencies
3. A safety update
4. Re-review of the proposed tradename, Yosprala

On March 14, 2016, the Applicant submitted a Class 2 resubmission (SDN 046) in response to the above December 16, 2014 CR letter.

Brief Discussion of Nonclinical Findings

The Applicant did not submit any nonclinical study report in this resubmission. Please refer to previous pharmacology reviews of NDA 205103 dated December 13, 2013 and November 21, 2014 for nonclinical information.

Recommendations

Approvability

From a nonclinical perspective, this NDA resubmission is recommended for approval.

Additional Non Clinical Recommendations

None

Studies Submitted

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

Studies Reviewed

N/A

Studies Not Reviewed

N/A

Previous Reviews Referenced

- Pharmacology review of NDA 205103 dated December 13, 2013 by Tamal Chakraborti, PhD
- Pharmacology review of NDA 205103 dated November 21, 2014 by Tamal Chakraborti, PhD

Labeling

The nonclinical sections of the proposed draft labeling of Yosprala® conforms to the content and format of labeling for human prescription drug and biological products under 21CFR201.57. However, the following revisions are recommended.

8.1 Pregnancy

Applicant's Version:

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

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.

Evaluation: The Applicant's proposed version appears to be acceptable. However, the aspirin data was moved before omeprazole data in order to be consistent with Sections 13.1 and 13.2 of the label.

Recommended Version:

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

Applicant's Version:

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about (b) (4) 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)*].

Evaluation: The Applicant's proposed version appears to be acceptable. However, multiples of human exposure values were corrected in appropriate places.

Recommended Version:

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 NONCLIICAL TOXICOLOGY

Applicant's Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 (b) (4) 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 (b) (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). 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 (b) (4) 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 138.0 mg/kg/day (about (b) (4) 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.

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 test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138.0 mg/kg/day (about (b) (4) 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.

Evaluation: 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.

Recommended Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Applicant's Version:

13.2 Animal Toxicology and/or Pharmacology

Aspirin

The acute oral 50% lethal dose in rats is about 1.5 g/kilogram (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 (b) (4) times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about (b) (4) 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 (b) (4) 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 138.0 mg/kg/day (about (b) (4) 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 (b) (4) 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.

Evaluation: The Applicant's proposed version appears to be acceptable. However, multiples of human exposure values were corrected in appropriate places.

Recommended Version:

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.

Integrated Summary and Evaluation

This Class 2 resubmission is in response to the Complete Response (CR) letter dated December 16, 2014. The Applicant did not submit any nonclinical study report in this submission. There are no nonclinical issues. Please refer to previous pharmacology reviews of NDA 205103 dated December 13, 2013 and November 21, 2014 for nonclinical information. From a nonclinical perspective, this resubmission is recommended for approval.

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/s/

TAMAL K CHAKRABORTI
08/05/2016

SUSHANTA K CHAKDER
08/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	205103
Supporting document/s:	036
Applicant's letter date:	June 30, 2014
CDER stamp date:	June 30, 2014
Product:	PA8140 and PA32540 (Yosprala®, Aspirin/Omeprazole) Tablets
Indication:	For use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Applicant:	POZEN, Inc.
Review Division:	DGIEP
Reviewer:	Tamal Chakraborti, Ph.D.
Supervisor:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, MD
Project Manager:	Stacy Barley, RN, M.S.N., M.H.A

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

1.1 INTRODUCTION 3
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 3
1.3 RECOMMENDATIONS 3

INTEGRATED SUMMARY AND EVALUATION 7

1 Executive Summary

1.1 Introduction

PA8140 and PA32540 are the code names for aspirin 81 mg/omeprazole 40 mg tablets and aspirin 325 mg/omeprazole 40 mg tablets, respectively. This Class 2 resubmission is in response to the Complete Response (CR) letter dated April 25, 2014 regarding facility inspections, labeling issues and safety update.

1.2 Brief Discussion of Nonclinical Findings

The Applicant did not submit any nonclinical study report in this submission. Please refer to pharmacology review of NDA 205103 dated December 13, 2013 for nonclinical information.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, this NDA resubmission is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

None

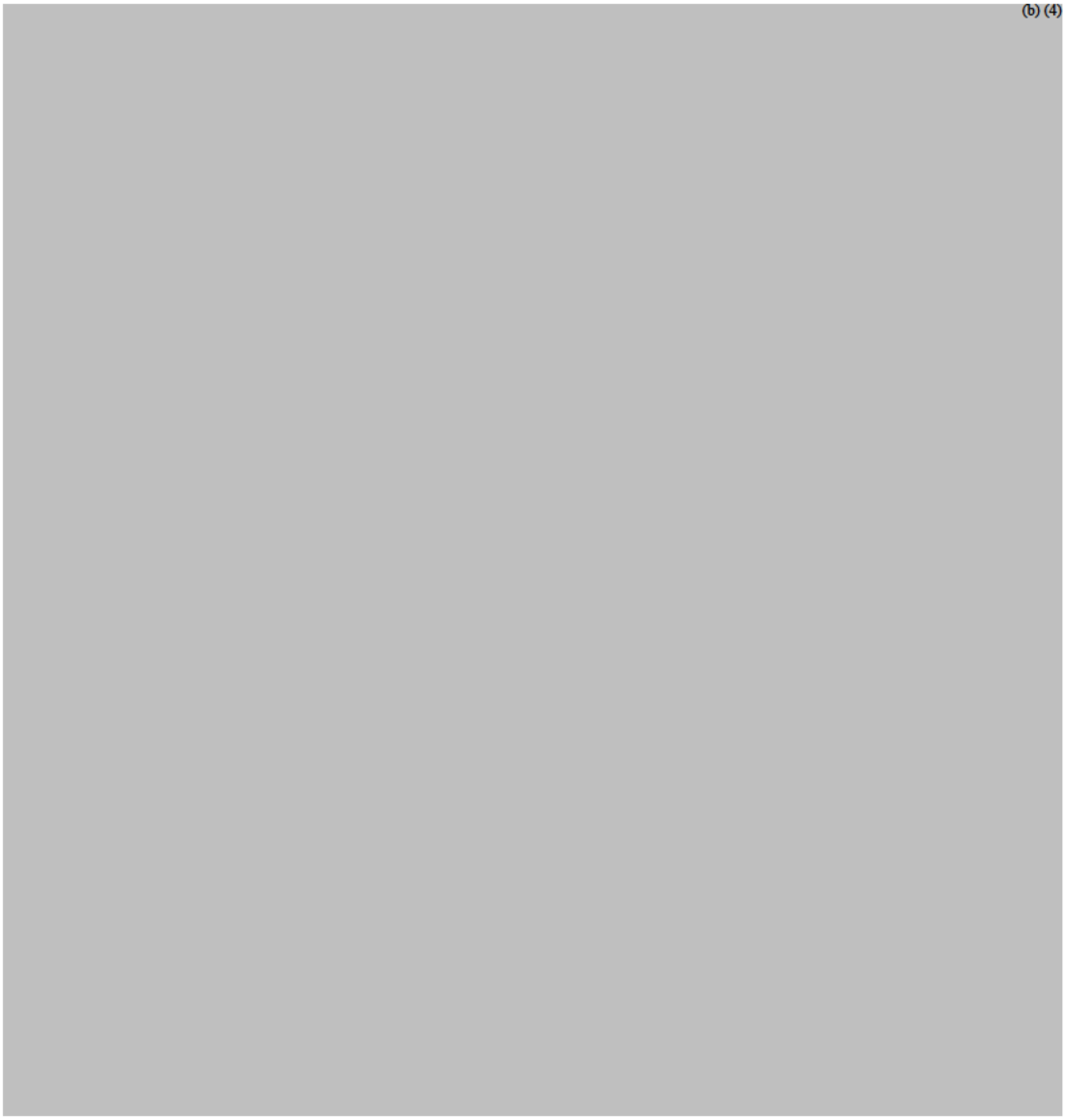
1.3.3 Labeling

The Applicant has accepted the nonclinical revisions that are contained in FDA's version of the labeling attached to the CR letter dated April 25, 2014. The current draft labeling of Yosprala® conforms to the content and format of labeling for human prescription drug and biological products under 21CFR201.57.

8.1 Pregnancy

Applicant's Version:

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



Evaluation: The Applicant deleted the duplicated sentence "Animal reproduction studies with omeprazole….human dose of 40 mg") from the beginning of the fourth paragraph on page 16 of the draft label (Section 8.1 Pregnancy) in the revised version dated October 30, 2014. The above sentence was duplicated in the second paragraph of Section 8.1 of the label. The Applicant's deletion of the above sentence and the proposed version is acceptable.

Recommended Version: N/A

Integrated Summary and Evaluation

This Class 2 resubmission is in response to the Complete Response (CR) letter dated April 25, 2014 regarding facility inspections, labeling issues and safety update. The Applicant did not submit any nonclinical study report in this submission.

The proposed labeling of Yosprala appears to conform to the specific requirements on content and format of relevant nonclinical sections of label for human prescription drugs under 21CFR 201.57. This resubmission is recommended for approval.

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/s/

TAMAL K CHAKRABORTI
11/21/2014

SUSHANTA K CHAKDER
11/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	205103
Supporting document/s:	001
Applicant's letter date:	March 25, 2013
CDER stamp date:	March 25, 2013
Product:	PA8140 and PA32540 (Yosprala®, Aspirin/Omeprazole) Tablets
Indication:	For use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Applicant:	POZEN, Inc.
Review Division:	DGIEP
Reviewer:	Tamal K. Chakraborti, Ph.D.
Supervisor:	Sushanta K. Chakder, Ph.D.
Division Director:	Donna Griebel, MD
Project Manager:	Stacy Barley, RN, M.S.N., M.H.A

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205103 are owned by POZEN, Inc. or are data for which POZEN, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 205103 that POZEN, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205103.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

1.1 INTRODUCTION 3
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 3
1.3 RECOMMENDATIONS 3

2 DRUG INFORMATION 13

2.1 DRUG 13
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS 14
2.3 DRUG FORMULATION 14
2.4 COMMENTS ON NOVEL EXCIPIENTS 22
2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN 24
2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN 30
2.7 REGULATORY BACKGROUND 30

3 STUDIES SUBMITTED 30

3.1 STUDIES REVIEWED 30
3.2 STUDIES NOT REVIEWED 30
3.3 PREVIOUS REVIEWS REFERENCED 30

4 PHARMACOLOGY 31

4.1 PRIMARY PHARMACOLOGY 31
4.2 SECONDARY PHARMACOLOGY 31
4.3 SAFETY PHARMACOLOGY 31

5 PHARMACOKINETICS/ADME/TOXICOKINETICS 32

5.1 PK/ADME 32
5.2 TOXICOKINETICS 34

6 GENERAL TOXICOLOGY 34

7 INTEGRATED SUMMARY AND SAFETY EVALUATION 34

8 APPENDIX/ATTACHMENTS 35

1 Executive Summary

1.1 Introduction

PA8140 and PA32540 are the code names for aspirin 81 mg/omeprazole 40 mg tablets and aspirin 325 mg/omeprazole 40 mg tablets, respectively. Aspirin is a non-steroidal anti-inflammatory drug (NSAID) and exhibits an anti-platelet effect by irreversibly inhibiting platelet thromboxane synthesis. Omeprazole is a proton pump inhibitor (PPI) and inhibits acid production in the stomach. PA8140 and PA32540 Tablets are designed to release the active ingredients in a coordinated manner. PA8140 and PA32540 Tablets release omeprazole immediately after ingestion and then expose the delayed release aspirin cor (b) (4) The Applicant developed PA Tablets to ensure that subjects who require chronic aspirin therapy will always receive a preceding PPI dose. PA Tablets are for oral administration on a once a day regimen. This is a 505(b)(2) application. The reference listed drugs (RLD) for this 505(b)(2) application are Ecotrin® (GlaxoSmithKline, aspirin) and Prilosec® (AstraZeneca, omeprazole).

1.2 Brief Discussion of Nonclinical Findings

The Applicant did not conduct any new nonclinical study with PA Tablets. The Agency agreed in a July 9, 2007 Pre-IND meeting (minutes dated August 8, 2007) that the Applicant could file a 505(b)(2) application relying on the Agency's previous findings of safety and publicly available information on the toxicology of aspirin and omeprazole to support the 505(b)(2) application. As per the above agreement with the Agency, the Applicant did not submit any nonclinical study report in this NDA. The Applicant provided summaries of the relevant nonclinical information available for aspirin and omeprazole in the published literature.

Aspirin and omeprazole exert their pharmacological activity through specific and different mechanisms. It is not expected that there will be any pharmacological interaction between these two drugs resulting in unexpected new toxicity. Neither aspirin nor omeprazole should have any effect on the absorption or metabolism of the other drug. Based on the available information, administration of aspirin with omeprazole is expected to cause the known toxicity of each of the individual drugs; no new types of toxicity or exacerbation of existing toxicities are anticipated. Overall, non-clinical information appears to adequately support the use of the product at the intended therapeutic dosage and in accordance with the proposed product labeling.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, this NDA is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The draft labeling of Yosprala® conforms to the content and format of labeling for human prescription drug and biological products under 21CFR201.57. However, the following changes are recommended as per the recommendations of the pediatric and maternal health staff (PMHS).

8.1 Pregnancy

Applicant's Version:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy:

(b) (4)

(b) (4)

Evaluation: The following changes are recommended as per the PMHS recommendations.

Recommended Version:

"8.1 Pregnancy

(b) (4)

Risk Summary

(b) (4)

Animal Data

(b) (4)

(b) (4)

(b) (4)

Applicant's Version:

(b) (4)

Evaluation: The following changes are recommended as per the PMHS recommendations.

Recommended Version:

8.4 Pediatric Use

Applicant's Version:

8.4 Pediatric Use:

Evaluation: As per the PMHS recommendation, juvenile toxicity data for esomeprazole should be incorporated.

Recommended Version:

"8.4 Pediatric Use:

(b) (4)

[redacted]

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's Version:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

(b) (4)

[redacted]

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Evaluation: The labeling of this section for aspirin was as per the aspirin professional labeling 21CFR343.80 and the labeling for omeprazole was adopted from the innovator's labeling of omeprazole (Prescribing Information for Prilosec). Therefore, no changes in the proposed labeling are recommended.

Recommended Version: None

13.2 Animal Toxicology and/or Pharmacology

Applicant's Version:

13.2 Animal Toxicology and/or Pharmacology:

Aspirin:

Omeprazole:

Evaluation: As per the PMHS recommendation based on FDAAA safety, the juvenile toxicity data of esomeprazole should be incorporated.

Recommended Version:

"13.2 Animal Toxicology and/or Pharmacology

Aspirin:

The acute oral 50 percent lethal dose in rats is about 1.5 g/kilogram (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 (b) (4) times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about (b) (4) 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 (b) (4) 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 138.0 mg/kg/day (about (b) (4) times the human doses on a body surface area basis).

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 esomeprazole/kg/day (about 17 to (b) (4) times a daily oral human dose of 40 mg on a body surface area basis). (b) (4) In addition, doses equal to or greater than 140 mg esomeprazole/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."

2 Drug Information

2.1 Drug

Aspirin

CAS Registry Number: 50-78-2

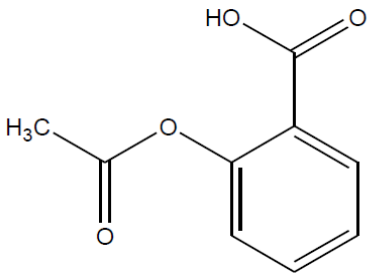
Generic Name: Aspirin

INN Name: Acetylsalicylic Acid

Chemical Name: 2-Acetoxybenzoic Acid

Molecular Formula/Molecular Weight: $C_9H_8O_4$/180.2

Structure:



Pharmacologic Class: Nonsteroidal anti-inflammatory drug (NSAID)

Omeprazole

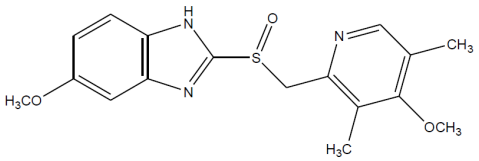
CAS Registry Number: 73590-58-6

Generic Name: Omeprazole

Chemical Name: (*RS*)-5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1*H*benzo[*d*]imidazole

Molecular Formula/Molecular Weight: $C_{17}H_{19}N_3O_3S$/345.4

Structure:



Pharmacologic Class: Proton pump inhibitor (PPI)

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 78,747 (PA32540/Aspirin/Omeprazole, Pozen, Inc.)
- IND 70,477 (Naproxen/Omeprazole, Pozen)
- NDA 22-511 (Vimovo®/Naproxen/Esomeprazole, AstraZeneca)
- NDA 19-810 (Prilosec®, Omeprazole, AstraZeneca)

2.3 Drug Formulation

PA8140 and PA32540 Tablets have been designed with an inner enteric coated (delayed release) core containing 81 mg or 325 mg of aspirin, USP and an outer film coat containing 40 mg of immediate release omeprazole, USP. Omeprazole, USP and aspirin, USP are the active ingredients of Prilosec® and Ecotrin®, respectively. Both

PA32540 and PA8140 Tablets consist of an aspirin core that is coated with (b) (4) film coats (b) (4) The following Figure (from page 4 of Section 3.2.P.2) shows the construction of the product.

Figure 1: Schematic of PA32540 and PA8140 Tablet (not to scale)

(b) (4)

PA8140 Tablets

PA8140 Tablets (81 mg aspirin/40 mg omeprazole) are oval, blue-green, film coated tablets printed with "81/40" in black on one side. The following Tables (from page 1-3 of Section 3.2.P.1) show the qualitative and quantitative composition of PA8140 Tablets and the qualitative composition of inactive ingredients used in PA8140 Tablets that are supplied (b) (4)

Table 1: Composition

Components	Quantity (mg per unit)	Function	Standard
(b) (4)			
Aspirin	(b) (4)	Active Ingredient	DMF
Cellulose Microcrystalline	(b) (4)	(b) (4)	NF
Starch	(b) (4)		NF
Silicon Dioxide Colloidal			NF
Stearic Acid	(b) (4		NF
(b) (4			(b) (4)
Triethyl Citrate			NF
(b) (4			(b) (4)
Omeprazole	40	Active Ingredient	USP
Polysorbate 80		(b) (4)	NF
Sodium Phosphate Dibasic Anhydrous			USP
(b) (4			(b) (4)

Components	Quantity (mg per unit)	Function	Standard
(b) (4)			
Carnauba Wax		(b) (4)	NF
(b) (4)			
(b) (4)			

Table 2: Qualitative composition of the components (b) (4)

(b) (4)

PA32540 Tablets

PA32540 Tablets (325 mg aspirin/40 mg omeprazole) are oval, blue-green, film coated tablets printed with "325/40" in black on one side. The following Tables (from page 1-3 of Section 3.2.P.1) show the qualitative and quantitative composition of PA32540 Tablets and the qualitative composition of inactive ingredients used in PA32540 Tablets that are supplied (b) (4)

Table 1: Composition

Components	Quantity (mg per unit)	Function	Standard
(b) (4)			
Aspirin		Active Ingredient	DMF
Cellulose Microcrystalline			NF
Starch			NF
Silicon Dioxide Colloidal			NF
Stearic Acid			NF
Triethyl Citrate			NF
Omeprazole	40	Active Ingredient	USP
Polysorbate 80			NF
Sodium Phosphate Dibasic Anhydrous			USP

Components	Quantity (mg per unit)	Function	Standard
(b) (4)			
Carnauba Wax	0.05	Polishing agent	NF
(b) (4)			

Table 2: Qualitative composition of the components (b) (4)

(b) (4)

2.4 Comments on Novel Excipients

(b) (4) The following table (from page 1 of Section 3.2.P.4) shows the list of compendial excipients.

Table 1 Specifications for pharmacopeial excipients in PA32540 and PA8140 Tablets

Excipient	Reference
Carnauba wax	NF
Cellulose microcrystalline (b) (4)	NF
Colloidal silicon dioxide	NF
Methacrylic acid copolymer dispersion	NF
Polysorbate 80	NF
(b) (4)	
Sodium Phosphate Dibasic Anhydrous	USP
Starch (b) (4)	NF
Stearic Acid	NF
Triethyl Citrate	NF

None of the excipients are of animal origin.

(b) (4)

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2.5 Comments on Impurities/Degradants of Concern

The specifications for PA8140 are shown in the following table (from page 1 of Section 3.2.P.5.1 of Submission dated August 1, 2013).

1. SPECIFICATIONS – PA8140 TABLETS

The quality control specifications for PA8140 Tablets are provided in this section.

Table 1: Quality Control Specifications

Test	Limit	Method
Appearance	Blue-Green, film-coated, oval tablet, printed with "81/40" in black on one side	P14100 - Visual inspection
Identification for Aspirin by HPLC/UV	Positive - The retention time for the aspirin peak is within (b)(4)% of the standard peak	929905 – HPLC/UV
Identification for Aspirin by FT-IR [a]	Positive	881700 – FT-IR
Assay for Aspirin by HPLC/UV	(b)(4)%	929905 – HPLC/UV
Uniformity of Dosage Units for Aspirin by HPLC/UV	Meets the requirements of the current USP	929905 – HPLC/UV
Related Substances for Aspirin by HPLC/UV	(b)(4) NMT (b)(4)% Individual NMT % Total NMT %	929905 – HPLC/UV
Identification for Omeprazole by HPLC/UV	Positive - The retention time for the omeprazole peak is within (b)(4)% of the standard peak	929906 – HPLC/UV
Identification for Omeprazole by TLC [a]	Positive	881600 - TLC
Assay for Omeprazole by HPLC/UV	(b)(4)%	929906 – HPLC/UV
Uniformity of Dosage Units for Omeprazole by HPLC/UV	Meets the requirements of the current USP	929906 – HPLC/UV
Related Substances for Omeprazole by HPLC/UV	Individual NMT (b)(4)% Total NMT %	929909 – HPLC/UV
Dissolution - Acid Resistance for Aspirin (0.1 N HCl)	Meets the requirements of the USP (NMT (b)(4)%)	929907 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm 120 minutes in 900 mL 0.1M hydrochloric acid at 37.0°C
Dissolution for Aspirin (pH 6.8)	1. NMT (b)(4)% at (b)(4)minutes 2. Meets the requirements of the current USP (Q = (b)(4)% at (b)(4)minutes)	929907 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm 120 minutes in 900 mL 0.1M hydrochloric acid at 37.0°C followed by media replacement with 900 mL phosphate buffer pH 6.8 at 37.0°C
Dissolution for Omeprazole (pH 7.4)	Meets the requirements of the current USP (Q = (b)(4)% at (b)(4) minutes)	929908 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm Media - 900 mL phosphate buffer pH 7.4 at 37.0°C

[a] Secondary test. Not tested routinely.

The specifications for PA32540 are shown in the following table (from page 1 of Section 3.2.P.5.1 of Submission dated August 1, 2013).

1. SPECIFICATIONS - PA32540 TABLETS

The quality control specifications for PA32540 Tablets are provided in this section.

Table 1: Quality Control Specifications

Test	Limit	Method
Appearance	Blue-Green, film-coated, oval tablet, printed with "325/40" in black on one side	P14100 - Visual inspection
Identification for Aspirin by HPLC/UV	Positive - The retention time for the aspirin peak is within (b) (4)% of the standard peak	846520 – HPLC/UV
Identification for Aspirin by FT-IR [a]	Positive	881700 – FT-IR
Assay for Aspirin by HPLC/UV	(b) (4)%	846520 – HPLC/UV
Uniformity of Dosage Units for Aspirin by HPLC/UV	Meets the requirements of the current USP	846520 – HPLC/UV
Related Substances for Aspirin by HPLC/UV	(b) (4) NMT (b) (4)% Individual NMT % Total NMT %	846520 – HPLC/UV
Identification for Omeprazole by HPLC/UV	The retention time for the omeprazole peak is within (b) (4)% of the standard peak	846630 – HPLC/UV
Identification for Omeprazole by TLC [a]	Positive	881600 - TLC
Assay for Omeprazole by HPLC/UV	(b) (4)%	846630 – HPLC/UV
Uniformity of Dosage Units for Omeprazole by HPLC/UV	Meets the requirements of the current USP	846630 – HPLC/UV
Related Substances for Omeprazole by HPLC/UV	Individual NMT (b) (4)% Total NMT %	846720 – HPLC/UV
Dissolution - Acid Resistance for Aspirin (0.1 N HCl)	Meets the requirements of the USP	883400 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm 120 minutes in 900 mL 0.1M hydrochloric acid at 37.0°C
Dissolution for Aspirin (pH 6.8)	1. NMT (b) (4)% at (b) (4) minutes 2. Meets the requirements of the current USP (Q = (b) (4)% at (b) (4) minutes)	883400 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm 120 minutes in 900 mL 0.1M hydrochloric acid at 37.0°C followed by media replacement with 900 mL phosphate buffer pH 6.8 at 37.0°C
Dissolution for Omeprazole (pH 7.4)	Meets the requirements of the current USP (Q = (b) (4)% at (b) (4) minutes)	846330 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm Media - 900 mL phosphate buffer pH 7.4 at 37.0°C

[a] Secondary test. Not tested routinely.

Aspirin:

The potential (b) (4) impurities for aspirin in PA32540 and PA8140 Tablets are presented in the Table below (from page 1 of Section 3.2.P.5). (b) (4)

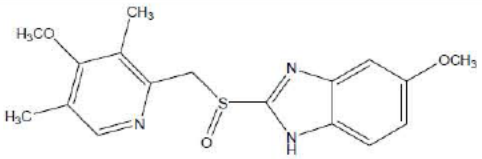
Table 1: Aspirin and Potential Aspirin Impurities in PA32540 and PA8140 Tablets

(b) (4)

Omeprazole:

The potential organic omeprazole impurities in PA32540 and PA8140 Tablets are presented in the Table below (from page 2 of Section 3.2.P.5). The predominant omeprazole degradation products observed in long term stability studies as well as accelerated stability studies (b) (4) relative retention times (RRT) of these impurities were determined to be (b) (4)

Table 2: Omeprazole and Potential Omeprazole Impurities in PA32540 and PA8140 Tablets

Name	Type	RRT	Chemical Structure	Chemical Name
Omeprazole	A	1.0		5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl] benzamidazole
[redacted]				(b) (4)

The proposed acceptance criteria for aspirin related substances are as follows: (b) (4) (b) (4) not more than (NMT) (b) (4)%, individual NMT (b) (4)%, and total NMT (b) (4)%. The proposed limits for aspirin related substances were set in compliance with ICH Q3B guidelines. The specifications were also set in consideration of the data available for the generally accepted limits (b) (4) in the USP Aspirin Delayed-Release Tablets. (b) (4) In addition, (b) (4) limit defined in the USP monographs for aspirin coated tablets is (b) (4)%. Therefore, the proposed specification of NMT (b) (4)% (b) (4) (b) (4) in the drug product does not appear to raise any safety concern from nonclinical perspective and is acceptable.

Acceptance criteria for omeprazole related impurities are as follows: individual NMT (b) (4)% and total NMT (b) (4)%. The specifications were set in consideration of the data available for the generally accepted limits for individual impurities for the USP Omeprazole Delayed Release Capsules. Related substances limits for individual related substances of NMT (b) (4)% and for total related substance of no more than (b) (4)% are proposed. The proposed limits for individual omeprazole related substances are in compliance with the ICH Q3B guidelines. The specifications for omeprazole related impurities are within the qualification threshold (ICHQ3B) and are acceptable from a nonclinical perspective.

2.6 Proposed Clinical Population and Dosing Regimen

As per the proposed label, Yosprala® tablets are indicated for patients (b) (4) The recommended dosage is one tablet daily. Each tablet contains 81 mg delayed release aspirin/40mg immediate release omeprazole or 325 mg delayed release aspirin/40mg immediate release omeprazole.

2.7 Regulatory Background

The following are the major milestones.

- Type B pre-IND meeting on July 9, 2007
- Type A meeting on January 31, 2012
- Type B pre-NDA meeting on April 23, 2012
- Type A meeting on August 21, 2012

3 Studies Submitted

As per the agreement with the Agency, the Applicant did not conduct any new non-clinical study with the product and did not submit any nonclinical study report in this application. The Applicant provided summaries of the relevant non-clinical information for aspirin and omeprazole available in the published literature to support this NDA as per the agreement with the Agency.

3.1 Studies Reviewed

N/A

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

Pharmacology review of NDA 19-810 (Omeprazole)

4 Pharmacology

4.1 Primary Pharmacology

Aspirin

Aspirin is an approved drug and has been in use in the US since 1965. Aspirin is a non-steroidal anti-inflammatory drug (NSAID) and is a potent inhibitor of both prostaglandin (PG) synthesis and platelet aggregation. It inhibits both cyclo-oxygenase 1 and 2 (COX-1 and COX-2) enzymes. The antiplatelet effect of aspirin is associated with inhibition of platelet aggregation and prolongation of the bleeding time. At higher doses, aspirin is an effective analgesic, anti-inflammatory and antipyretic agent due to its inhibition of COX-2 and inducible nitric oxide synthase (iNOS).

Omeprazole

Omeprazole is marketed in the US as Prilosec®, and is indicated for the short-term treatment of active duodenal and gastric ulcer, gastroesophageal reflux disease (GERD), heartburn, for treatment and to maintain healing in erosive esophagitis (EE), and for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis). Omeprazole belongs to a class of anti-secretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H^+, K^+)-ATPase enzyme system located on the luminal surface of the gastric parietal cell. Omeprazole protects the gastric mucosa against aspirin- and ethanol-induced injury (Konturek SJ, et al., 1983, Digestion, 27:159-164). The benzimidazole proton pump inhibitors (PPI) are weakly basic compounds and become increasingly protonated upon entering an acidic environment in the stomach. In the acidic environment of the stomach, the PPIs undergo intramolecular rearrangement into the pharmacologically active entities, a cyclic sulfenamide and/or the sulfenic acid. The reactive cyclic sulfenamide and/or the sulfenic acid bind covalently to accessible cysteine (Cys) thiols such as Cys813 or Cys822 on the luminal surface of proton pumps thereby permanently inactivating them (Lambrecht N, et al., 1998, J Biol Chem, 273:13719-13728; Qaisi AM, et al., 2006, J Pharm Sci, 95:348-391; Tutunji MF, et al., 2006, J Pharm Sci, 96:196-208). Due to the covalent nature of the (H^+, K^+)-ATPase inhibition, restoration of acid production in the stomach mainly occurs through the *de novo* synthesis of new proton pumps, the half-life of which is approximately 50 hours (Litalien C, et al., 2005, Clin Pharmacokinet, 44:441-466; Gedda K, et al., 1995, Gastroenterol, 109:1134-1141).

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Aspirin

The Applicant did not conduct any nonclinical pharmacokinetic (PK) studies with aspirin or PA Tablets. The plasma half-lives of salicylate in the rat, rabbit and dog are approximately 6, 5 and 10 hours, respectively (Graham GG, et al., 2004, In, Pharmacokinetics and metabolism of aspirin. In, Aspirin and Related Drugs. KD Rainsford (ed.), CRC Press, New York, NY, Chapter 4, pp 97-155). In humans, aspirin is well absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is rapidly hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing. The plasma half-life for aspirin is approximately 15 minutes and that for salicylic acid is 2-3 hours at low doses and about 12 hours at usual antiinflammatory doses.

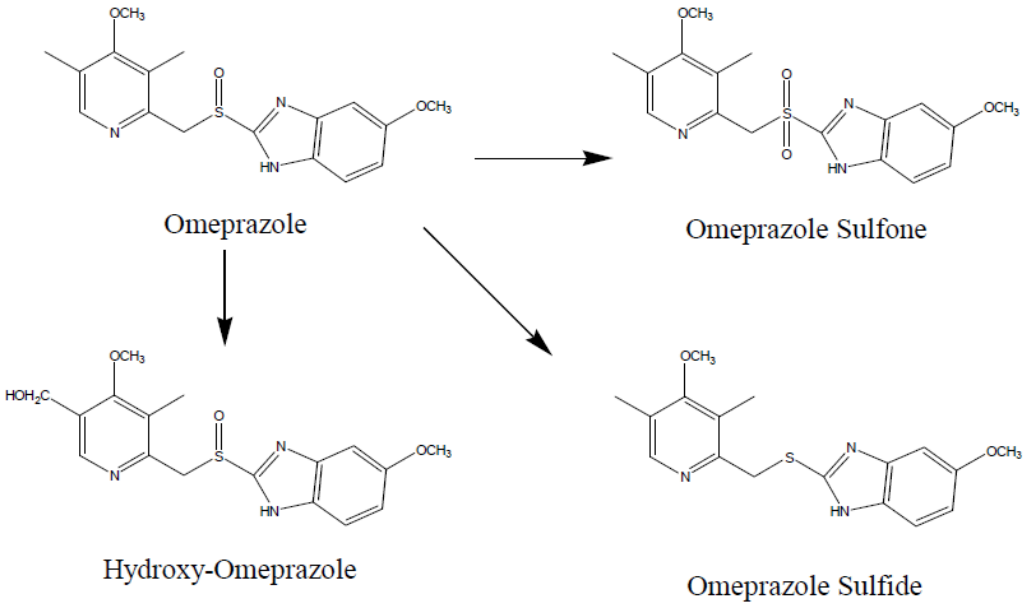
Omeprazole

The Applicant did not perform any nonclinical pharmacokinetic study with omeprazole or PA Tablets. However, the Applicant conducted studies under IND 70477 in rats to examine whether any unique metabolite profiles were formed in rats secondary to dosing immediate-release ^{14}C-labeled omeprazole (b) (4) compared to immediate-release ^{14}C-labelled omeprazole (b) (4) (Pozen Study PN200-T1, IND 70477 SDN 020 dated April 28, 2006). (b) (4) The qualitative metabolite profile was the same for both treatment groups; (b) (4)

After oral dosing, omeprazole was rapidly absorbed in mice, rats and dogs and was readily distributed into different tissues. The T_{max} values were 10, 15, 5-15 and 13.8 minutes in the mouse, rat, dog and human, respectively. The oral bioavailability was about 5% in the fed and 15-20% in the starved rats of either sex. In humans, the systemic bioavailability was approximately 53% (Pilbrant A and C Cederberg, 1985, Scand J Gastroenterol Suppl., 108:113-20). The average total plasma clearance of omeprazole was 110, 70, 10, and 530 mL/min in the male rat, female rat, dog and human, respectively. Omeprazole was 87.5, 90 and 95.7% bound to plasma proteins in rat, dogs and humans, respectively. High concentrations of total radioactivity were found in the gastric mucosa, biliary tree, intestinal contents, urinary bladder, liver and kidneys with the lowest concentration in the brain following oral or intravenous (IV) administration of ^{14}C-labelled omeprazole (Prescribing Information, Prilosec® 2011). Cytochrome P4502C19 (CYP2C19) is the key enzyme involved in the formation of the hydroxy-metabolite, a major metabolite of omeprazole (Prescribing Information, Prilosec® 2011; Andersson T et al., 1990, Eur J Pharmacol, 39:195-197). The formation

of the sulfone (primary metabolite) metabolite was mediated by CYP3A4. Omeprazole induced CYP1A1/2 in human hepatocytes and inhibited CYP2C19. Omeprazole is extensively metabolized in the mouse, rat, dog and human (Regårdh CG, et al., 1985, Scand J Gastroenterol Suppl., 108:79-94). The metabolites were rapidly eliminated by biliary and urinary excretion with less than 0.1% of the administered dose excreted into the bile or the urine as parent drug. At least ten metabolites were isolated in the urine samples from each species (as shown in the following Figure from page 12 of Section. 2.4). Three metabolites were the sulfone, the sulfide and the hydroxy-metabolite. These metabolites had very little or no anti-secretory activity.

Figure 2: Metabolic pathways of omeprazole



The sulfone and sulfide metabolites have been identified in the human plasma. In nonclinical studies, the identified metabolites corresponded to 50% (rat) and 70% (dog) of the amounts excreted in the 0 to 24h urine; the remaining 30 to 50% of that excreted in the urine was unidentified. In mice, rats, dogs and humans, urinary excretion accounted for 56% and 43%, 38% and 76%, respectively, while fecal excretion accounted for 28%, 49%, 55% and 18%, respectively. The elimination half lives in the rat, dog and man were approximately 60 minutes. Omeprazole has been reported to inhibit P-glycoprotein (P-gp) in Caco-2 and L-MDR1 cells.

The Applicant did not conduct any new pharmacokinetic study with PA Tablets or co-administration of aspirin and omeprazole. As per the Applicant, the two components (aspirin and omeprazole) in PA Tablets exert their pharmacological activity through very specific and different mechanisms. It is therefore not anticipated that there will be any direct and/or adverse pharmacological interaction between aspirin and omeprazole. The Applicant has conducted a clinical trial in healthy volunteers demonstrating that there was no pharmacokinetic interaction between enteric-coated aspirin 325 mg and 40 mg

of immediate-release esomeprazole (Niazi M, et al., 2009, Int J Clin Pharmacol Ther, 49:169-176).

5.2 Toxicokinetics

N/A

6 General Toxicology

The Applicant did not conduct any new toxicology study with PA Tablets. Publicly available information on the toxicology of aspirin and omeprazole from the published literature were submitted to support this NDA as per the agreement with the Agency.

The Applicant stated that there are no known interactions between aspirin and omeprazole that might cause unexpected toxicity as a result of their co-administration. It is to be noted that omeprazole in the PA Tablets formulation is not enteric coated. The nonclinical toxicology programs for Prilosec® marketing approval used non-enteric coated (b) (4) omeprazole (NDA 19-810, FDA approval package). The Applicant provided summary of toxicology studies for non-enteric coated (b) (4) omeprazole in support of the non-enteric coated (b) (4) omeprazole formulation in PA tablets. Please refer to pharmacology review of NDA 19810 (FDA approval package, 1989) and NDA 22056 dated August 9, 2007 for nonclinical toxicology information for omeprazole.

7 Integrated Summary and Safety Evaluation

The Applicant did not conduct any new nonclinical study with PA Tablets. As per the agreement with the Agency, the Applicant submitted publicly available nonclinical information for aspirin and omeprazole from the published literature to support this 505(b)(2) application. There are no known interactions between aspirin and omeprazole that would indicate any novel nonclinical issues as a result of their co-administration. As agreed with the Agency in the Pre-IND meeting on July 9, 2007 (minutes dated August 8, 2007), the available nonclinical information from the summary basis of approvals, labeling and available published literature for aspirin and omeprazole was considered adequate to support this 505(b)(2) application.

Aspirin is an approved drug. Omeprazole is also approved for the treatment of gastroesophageal reflux disease (GERD). The Applicant's proposed dose for each drug in PA Tablets is the approved dose for each drug. As mentioned above, the Agency's previous findings of safety together with the published nonclinical information for aspirin and omeprazole have been relied on to support this 505(b)(2) NDA.

Aspirin and omeprazole exert their pharmacological activity through specific and different mechanisms. It is not expected that there will be any pharmacological interaction between these two drugs resulting in unexpected new toxicity. Neither

aspirin nor omeprazole should have any effect on the absorption or metabolism of the other drug. Based on the available information, administration of aspirin with omeprazole is expected to cause the known toxicity of each of the individual drugs; no new types of toxicity or exacerbation of existing toxicities are anticipated. Overall, non-clinical information appears to adequately support the use of the product at the intended therapeutic dosage and in accordance with the proposed product labeling. From a nonclinical standpoint, this 505(b)(2) application satisfies the criteria for marketing authorization of PA8140 and PA32540 Tablets. Therefore, this NDA is recommended for approval from a nonclinical perspective.

8 Appendix/Attachments

None

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/s/

TAMAL K CHAKRABORTI
12/13/2013

SUSHANTA K CHAKDER
12/13/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205103 **Applicant: Pozen, Inc.** **Stamp Date: 3/25/13**

Drug Name: (b) (4) **(PA8140 and PA32540 (Aspirin/Omeprazole) Tablets** **NDA Type: New 505(b)(2) NDA** **Submit Date: 3/25/13**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			As per an agreement (meeting minutes dated August 8, 2007) with the Agency, no new non-clinical studies were conducted. The applicant provided a full review of the relevant non-clinical literature in Module 2.4
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		The proposed labeling sections relevant to nonclinical studies may need to be revised during the labeling review.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant. **N/A**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None**

Tamal K. Chakrabortit, Ph.D. — April 29, 2013
Reviewing Pharmacologist — Date

Sushanta K. Chakder, Ph.D. — April 29, 2013
Supervisor — Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

TAMAL K CHAKRABORTI
04/29/2013

SUSHANTA K CHAKDER
04/29/2013