

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205103Orig1s000

OTHER REVIEW(S)

M E M O R A N D U M

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

DATE: August 19, 2016

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products, Office of Drug Evaluation III,
Office of New Drugs

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Young Moon Choi, Ph.D.
Deputy Director (Acting)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: (b) (4)
(b) (4)
(b) (4) for NDA 205103

Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portions of the PA8140-104 and PA32540-119 studies (under NDA 205103) (b) (4)

(b) (4) Based on the inspection findings, OSIS recommends accepting the analytical data from the PA8140-104 and PA32540-119 studies for further Agency review.

Studies Audited during this Inspection:

Study number: PA8140-104 (NDA 205103)

Study title: "A Single-Dose Randomized Crossover Study to Assess the Intrasubject Variability of Acetylsalicylic Acid from Administration of Three Tablets (Dosed Concurrently) of PA8140 and to Evaluate the Relative Bioavailability of Three Tablets (Dosed Concurrently) of Two Formulations of PA8140 with the Partial Reference-Replicated 3-Way Design and the Reference-Scaled Average Bioequivalence

Approach."

Sample Analysis: Analysis of human plasma samples began on 07 January 2016 and was completed on 17 January 2016.

Study number: PA32540-119 (NDA 205103)

Study title: "A Single-Dose Randomized Crossover Study to Assess the Intrasubject Variability of Acetylsalicylic Acid from Administration of PA32540 and to Evaluate the Relative Bioavailability of Two Formulations of PA32540 with the Partial Reference-Replicated 3-Way Design and the Reference-Scaled Average Bioequivalence Approach."

Sample Analysis: Analysis of human plasma samples began on 22 February 2016 and was completed on 07 March 2016

OSIS scientist Hasan Irier, Ph.D. conducted an inspection of the bioanalytical portions of the studies specified above (b) (4). The audit covered the bioanalytical method validation and the PA8140-104 and PA32540-119 sample analyses for acetylsalicylic acid. The audit also included a thorough review of facilities, equipment, study records and correspondences, and interviews and discussions with (b) (4) management and staff. At the conclusion of the inspection, no Form FDA 483 observations were issued.

Conclusion:

Based on the inspectional findings, (b) (4) bioanalytical study conducted (b) (4) this OSIS reviewer concluded that the data from the PA8140-104 and PA32540-119 studies are reliable. Therefore, OSIS recommends accepting the analytical portions of the PA8140-104 and PA32540-119 studies for further (FDA) Agency review.

Hasan A. Irier, Ph.D.
OSIS, DGDBE

Final Site Classification:

NAI -
FEI:

(b) (4)

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Haidar/Turner-Rinehardt/Nkah/Fenty-Stewart

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au/Irier

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

Draft: HAI 08/15/16,

Edits: SA 08/15/16, YMC 08/17/16, HAI 8/19/16

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good

Laboratory/ [REDACTED] gram/ANALYTICAL

SITES/ [REDACTED]

(b) (4)

OSI file 38

FACTS: [REDACTED]

(b) (4)

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/s/

HASAN A IRIER
08/19/2016

YOUNG M CHOI
08/19/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 205103
Product Name: Yosprala (aspirin/omeprazole)

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/2017</u>
	Study/Trial Completion:	<u>04/2017</u>
	Final Report Submission:	<u>06/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The drug's safety profile has been adequately assessed in the pre-approval program.

However, because this product contains non-enteric coated omeprazole which may be unstable in acidic pH, there is residual uncertainty regarding potential omeprazole degradants in the acidic pH of the stomach. To address this residual uncertainty an in vitro study will be conducted to characterize and quantify the degradants of immediate release omeprazole of Yosprala at various pH ranges (i.e., pH 1, 1.5, 2, 2.5, 3, 3.5, 4) following a minimum of 1 hour of exposure at 37°C and to evaluate the differences in the profiles across the pH range; the applicant should submit the chromatograms and summary of quantitative data generated in the study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See Response to 1 above.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See response to 1 above.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
in vitro study to evaluate degradants that could be formed *in vivo* in gastric acid.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 205103
Product Name: Yosprala (aspirin/omeprazole)

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/2017</u>
	Study/Trial Completion:	<u>03/2018</u>
	Final Report Submission:	<u>06/2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

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

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See Response to 1 above.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See Response to 1 above.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
a clinical PK study
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

MIMI T PHAN
09/14/2016

ANIL K RAJPAL
09/14/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 205103	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Yosprala Established/Proper Name: aspirin/omeprazole Dosage Form: tablets Strengths: aspirin 81 mg/omeprazole 40 mg; aspirin 325 mg/omeprazole 40 mg		
Applicant: Aralez Pharmaceuticals R&D Inc.		
Date of Receipt: March 25, 2013; CR issued April 25, 2014; Resubmission Received June 30, 2014; CR issued December 16, 2014; Resubmission Received on March 14, 2016.		
PDUFA Goal Date: September 14, 2016		Action Goal Date (if different):
RPM: CAPT Mimi T. Phan		
Proposed Indication(s): <ul style="list-style-type: none">• Secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin associated gastric ulcers.• Decreasing the risk of developing aspirin associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (≥ 55) or documented history of gastric ulcers.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
OTC Monograph for Aspirin (21 CFR 343.80)	Nonclinical section 13 Clinical Pharmacology sections 4, 7, 8, 12 Clinical sections 5, 6, 8, 14
NDA 019810 Prilosec (omeprazole) Capsules	Nonclinical section Clinical Pharmacology sections 7, 8, 12 Clinical sections 5, 6, 8

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The bridging was established through bioequivalent (BE) study for aspirin component and relative bioavailability (BA) study for omeprazole component.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Prilosec (omeprazole)	NDA 19810	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph: Ecotrin (aspirin)

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Prilosec NDA 19810

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new fixed-combination and indication, to decrease the risk of developing gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

If this application relies only on non-product-specific published literature, answer “N/A”
If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6147103, 6150380, 6166213, 6191148

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s): 6147103, 6150380, 6166213, 6191148

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) *Patent number(s):* 6147103, 6150380, 6166213, 6191148

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): AstraZeneca LP July 22, 2013; Merck July 22, 2013

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

MIMI T PHAN
09/13/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: August 3, 2016 **Date Consulted:** May 11, 2016

From: Christos Mastroyannis, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS,
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Division Director,
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Yosprala (aspirin and omeprazole) delayed-release tablets, for oral use

NDA: 205103

Applicant Pozen, Inc

Subject: Maternal Health Labeling Recommendations as per the Pregnancy and Lactation Labeling Rule (PLLR) for Labeling Conversion

Indications: Yosprala is a combination of aspirin, an anti-platelet agent and nonsteroidal anti-inflammatory drug (NSAID), and omeprazole, a proton pump inhibitor (PPI), 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.

The aspirin component of YOSPRALA is indicated for:

- reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli,
- reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris,
- reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris,
- use in patients who have undergone revascularization procedures (Coronary Artery Bypass Graft [CABG] or Percutaneous Transluminal Coronary Angioplasty [PTCA]) when there is a pre-existing condition for which aspirin is already indicated.

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

Materials Reviewed:

- June 1, 2016, Pozen's response to the DPMH's information request of May 12, 2016
- DGIEP consult request to DPMH for Yosprala Tablets, NDA 205103. May 11, 2016. DARRTS Reference ID 3929558.
- March 14, 2016, Pozen's Resubmission-Response to Complete Response Action Letter
- Labeling for Prilosec, NDA 022056. Labeling last revised on February 3, 2016, Drugs@FDA.
- Labeling for Aggrenox (Aspirin/Dipyridamol), NDA 20884. Labeling last revised on November 9, 2015, Drugs@FDA.
- DPMH review. Prilosec (omeprazole magnesium) delayed-release oral suspension, NDA 022056. Christos Mastroyannis, M.D. January 15, 2016. DARRTS Reference ID 3873309.
- Vimovo (naproxen/esomeprazole) delayed-release tablets. NDA 22511/s-018. Christos Mastroyannis, M.D. March 2, 2016. DARRTS Reference ID 3900270.
- OSE/DEPI-1 review (Epidemiology: Literature Review to recommend if literature supports absence of a signal for increased risk of congenital malformations and PPIs by Robert Campbell on January 15, 2014

Consult Question: DGIEP requests assistance with labeling review regarding the Pregnancy and Lactation Labeling Rule (PLLR) requirements for Yosprala (aspirin and omeprazole) delayed-release tablets, for oral use.

INTRODUCTION

DGIEP consulted the Division of Pediatric and Maternal Health (DPMH) on May 11, 2016, to review the Pregnancy and Lactation sections of labeling for Yosprala (aspirin and omeprazole) delayed-release tablets to ensure compliance with the Pregnancy and Lactation Labeling Rule

(PLLR) formatting requirements and to provide comments to be included in the labeling that will be sent to the applicant.

REGULATORY HISTORY

On March 25, 2013, Pozen, Inc. submitted a 505(b)(2) new drug application (NDA) for Yosprala. The Agency issued a complete response (CR) letter on April 25, 2014 due to several deficiencies with the application, including manufacturing facility inspection deficiencies and labeling deficiencies. Pozen, Inc. responded to the CR letter on June 30, 2014, but the Agency issued a second CR letter on December 16, 2014 due to continued deficiencies. On March, 14, 2016, Pozen Inc. submitted a Class 2 Resubmission in response to the FDA CR letter from December 2014. In addition to correcting their deficiencies, the applicant updated the labeling to the PLLR format. Yosprala 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 ulcers. The reference listed products for Yosprala include Ecotrin (aspirin), which is over-the-counter, and Prilosec (omeprazole), NDA 19810, which was approved September 14, 1989.

BACKGROUND

Drug Characteristics

The active ingredients of Yosprala are aspirin (acetylsalicylic acid), an antiplatelet and nonsteroidal anti-inflammatory drug (NSAID); and omeprazole [a proton pump inhibitor (PPI)]. The applicant proposes two strengths for Yosprala to be marketed. One contains 81 mg delayed release aspirin and 40 mg immediate release omeprazole and the second one contains 325 mg delayed release aspirin and 40 mg immediate release omeprazole printed with 81/40 and 325/40 (fixed dose omeprazole). The excipients used in the formulation of Yosprala are all inactive and United States Pharmacopeia/National Formulary (USP/NF) defined.

Aspirin

Aspirin is marketed under a monograph. Aspirin is responsible for the inactivation of cyclooxygenase via acetylation (similar action to NSAIDs). At higher doses, aspirin reversibly inhibits the formation of prostaglandin I₂ (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation. Aspirin has a molecular weight of 180.16 Daltons and a half-life of 0.35 hours. Protein binding of aspirin is 90% at low concentrations (<100mcg/mL) and 75% at high concentrations (>400mcg/mL). Ecotrin is an over the counter (OTC) drug marketed under an OTC monograph and thus no information exists to which an NDA can reference. Aggrenox marketed under an NDA (NDA 020884 approved on November 22, 1999) was selected by DGIEP Pharmacology/Toxicology because it contains relevant animal data on aspirin exposure. The existing labeling for Aggrenox, in section 5 Warnings and Precautions, states the following adverse events that are associated with aspirin use in adults including: serious gastrointestinal reactions (inflammation, bleeding, ulceration and perforation), renal failure, and hepatic impairment, etc.

Omeprazole

Omeprazole suppresses gastric acid secretion by specific inhibition of the [H⁺/K⁺]-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is

dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Omeprazole has a molecular weight of 345.4 Daltons, a half-life of one hour, and protein binding of 95%. The existing labeling for Prilosec, in the section 5 Warnings and Precautions, states the following adverse events that are associated with omeprazole use in adults including: acute interstitial nephritis, *Clostridium Difficile*- associated diarrhea, fractures, cyanocobalamin deficiency and hypomagnesemia etc..

Current State of Labeling for Pregnancy and Lactation

Aspirin

The pregnancy section of current Aggrenox labeling notes that aspirin is a category D drug. There is a Warnings and Precautions section that describes the fetal harm that can occur with aspirin administration (failure of the fetal ductus arteriosus to close, low birth weight, increased incidence of intracranial hemorrhage in premature infant, stillbirth and neonatal death). There is no boxed warning, and there are no known drug-drug interactions with hormonal contraceptives. The current aspirin labeling recommends that caution be used when the drug is given to a nursing woman. No aspirin labeling exists in PLLR format.

Omeprazole

The pregnancy section of current Prilosec labeling, which was revised February 2016, notes that available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester use of omeprazole. There is no information related to pregnancy in Warnings and Precautions or in the boxed warning. There are no known drug-drug interactions between omeprazole and hormonal contraceptives. The Lactation section of current Prilosec labeling does not recommend against breastfeeding.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*”, also known as the Pregnancy and Lactation Labeling Rule (PLLR)¹. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) is removed from all prescription drug and biological product labeling and a new format will be required for all drug products that are subject to the 2006 Physician Labeling Rule (PLR)², to include information about the risks and benefits of using these products during pregnancy and lactation.

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling in

¹ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

² Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

order to provide clinically relevant information for prescribing decisions and to comply with PLLR regulatory requirements.

REVIEW

Pregnancy

Nonclinical experience

Current Yosprala labeling provided by the applicant includes data from animal reproduction studies that were conducted for approval of Aggrenox (aspirin/dipyridamole) and omeprazole. No new nonclinical studies have been submitted for this NDA.

Aspirin

Aspirin produced a spectrum of developmental anomalies when administered to Wistar rats as single, large doses (500- to 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 cranio-rachischisis, 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.³

Omeprazole and esomeprazole

The nonclinical experience data on omeprazole and esomeprazole have been previously reviewed and remain unchanged. For more details, the reader is referred to the DPMH review of Prilosec by Christos Mastroyannis, MD and current Prilosec labeling revised on February 3, 2016 (see Materials Reviewed above).

The reader is referred to the Nonclinical Review by Tamal Chakraborti, PhD for further details of animal reproduction studies conducted with aspirin and omeprazole.⁴

Applicant's Review of Literature

The applicant's and DPMH conducted a search of PubMed, Embase, ReproTox and TERIS databases regarding Yosprala, and they did not identify any publications.

An information request by the Division asked the applicant to provide a review and summary of all available published literature regarding aspirin use in pregnant and lactating women, but not for omeprazole, so the literature review by the applicant refers only to aspirin. Data on omeprazole and esomeprazole have been previously reviewed by DPMH and remain unchanged as they appear in current labeling.

Aspirin

The applicant performed a PubMed search using the terms "pregnancy" and "aspirin" to identify published literature regarding aspirin use in pregnant women. Over 2000 publications were identified. The applicant applied a filter to limit the search to include only the most recent

³ Aggrenox existing labeling of November 9, 2015. Drugs@FDA.

⁴ Pharmacology/Toxicology Review. Yosprala (aspirin/omeprazole) tablets. August 5, 2016. DARRTS Reference ID 3968483

publications (last 25 years), in humans and in English. The subset of articles was then further limited by utilizing the following search terms: review articles (487), clinical studies (225) comparative studies (90), randomized controlled (160) and controlled trials (185), guidelines (15) / practice guidelines (14) and meta-analysis (48). Series of less than 100 subjects, individual case reports and review articles, which reiterated identical information were reviewed but not included in the summary. An emphasis was placed on practice guidelines and societal recommendation statements. Studies that evaluated pre-pregnancy utilization and uses for those outside of the Yosprala indication were reviewed for safety, but were also excluded from the summary.

Aspirin has been considered for use in pregnancy in a variety of conditions. Most commonly, aspirin has primarily been used for prevention of preeclampsia. However, aspirin has also been used in the management of antiphospholipid antibody conditions and recurrent spontaneous abortions; although aspirin is not approved for use in these conditions. A large volume of literature exists regarding the efficacy and safety of aspirin. The applicant summarized the following findings in their information request response:⁵

- Aspirin use has been demonstrated in a preponderance of studies to benefit patients with preeclampsia and associated conditions reducing risks.
- Low-dose aspirin use in the first trimester is controversial and may be associated with an increased risk of gastroschisis.
- Low-dose aspirin use during pregnancy seems to have little or no impact on the developing fetus in the second and third trimester and does not appear to impact postnatal development.
- Maternal risks during pregnancy were low or absent with no demonstrated increased risk of maternal bleeding or placental abruption.
- In the majority of studies, low-dose aspirin was utilized, and thus there are limited data regarding higher doses.

Additionally, a number of medical associations have adopted guidelines for aspirin use in pregnancy.

- The U.S. Preventive Services Task Force recommends the use of low-dose aspirin (81 mg/day) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia.⁶
- The American College of Obstetricians and Gynecologists recommends initiating use of low-dose aspirin (60 to 80 mg/day) during the late first trimester to prevent preeclampsia in women with a medical history of early-onset preeclampsia and preterm delivery (34 weeks) or history of preeclampsia in more than one previous pregnancy.⁷

⁵ Applicant's response to the Division's information request of May 12, 2016, June 1, 2016

⁶ www.uspreventiveservicestaskforce.org/: Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality From Preeclampsia: Preventive Medication, September 2014

⁷ American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Washington, DC: American College of Obstetricians and Gynecologists; 2013. Available at: <http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy>. Practice Advisory on Low-Dose Aspirin and Prevention of Preeclampsia: Updated Recommendations. Retrieved July 7, 2016

- The World Health Organization recommends the use of low-dose aspirin (75 mg/day) starting as early as 12 to 20 weeks of gestation for high-risk women (i.e., those with a history of preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, or multifetal pregnancies). It states that there is limited evidence regarding the benefits of low-dose aspirin in other subgroups of high-risk women.⁸
- The National Institute for Health and Care Excellence recommends that women at high risk for preeclampsia (i.e., those with a history of hypertension in a previous pregnancy, chronic kidney disease, autoimmune disease, type 1 or 2 diabetes, or chronic hypertension) take 75 mg/day of aspirin from 12 weeks until delivery. It recommends the same for women with more than one moderate-risk factor (first pregnancy, age \geq 40 years, pregnancy interval \geq 10 years, body mass index \geq 35 kg/m², family history of preeclampsia, or multifetal pregnancies).⁹
- The American Heart Association and the American Stroke Association recommend that women with chronic primary or secondary hypertension or previous pregnancy-related hypertension take low-dose aspirin from 12 weeks until delivery.^{10,11}
- The American Academy of Family Physicians recommends low-dose aspirin (81 mg/d) after 12 weeks of gestation in women who are at high risk for preeclampsia.^{4,12}

A meta-analysis by Kozer, *et al.*,¹³ of the clinical literature did not find an overall increase in risk of congenital defects associated with first trimester use of aspirin. Some case-control studies reported associations between human congenital malformations and aspirin use early in gestation, but these studies did not report a consistent outcome attributable to drug use. One case-control study, for example, reported an increase in cleft palate among offspring of aspirin users¹⁴, a second found an increase in anencephaly, craniorachischisis, microphthalmia, amniotic band syndrome, and cleft palate¹⁵, and a third found an increased stillbirth rate and reduced birth weight among offspring of women who used aspirin intermittently during pregnancy but no increase in congenital malformations.¹⁶

⁸ World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: WHO; 2011. Available at: http://apps.who.int/iris/bitstream/10665/44703/1/9789241548335_eng.pdf. Retrieved July 7, 2016.

⁹ National Institute for Health and Care Excellence. Quality statement 2: Antenatal assessment of pre-eclampsia risk. In: Hypertension in pregnancy. Manchester: NICE; 2013. p. 16-9. Available at: <https://www.nice.org.uk/guidance/qs35/resources/hypertension-in-pregnancy-2098607923141>.

¹⁰ stroke.ahajournals.org/content/early/2014/.../STR.000000000000024.full.pdf Stroke, by WN Kernan - 2014

¹¹ stroke.ahajournals.org/content/early/.../01.str.0000442009.06663.48.full.pdf Stroke, by C Bushnell - 2014

¹² www.aafp.org/.../20140910lowdoseasa.html. American Academy of Family Physicians Sep 10, 2014 -

¹³ Kozer E, Nikfar S, Costei A, Boskovic R, Nulman I, Koren G: Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. *Am J Obstet Gynecol* 187:1623-1630, 2002

¹⁴ Saxen I: Associations between oral clefts and drugs taken during pregnancy. *Int J Epidemiol* 4:37-44, 1975.

¹⁵ Hernandez RK, Werler MM, Romitti P, Sun L, Anderka M, and the National Birth Defects Prevention Study. 2012. Nonsteroidal anti-inflammatory drug use among women and the risk of birth defects. *Am J Obstet Gynecol* 206(3): 228.e1-8

¹⁶ Turner G and Collins E: Fetal effects of regular salicylate ingestion during pregnancy. *Lancet* 2:338-9, 1975

DPMH's Review of Literature

Aspirin

DPMH searched PubMed, Embase, ReproTox and TERIS databases for information regarding aspirin and use during pregnancy. Additional published information to what the applicant provided was identified.

ReproTox¹⁷ states: "High-dose aspirin exposure in experimental animal studies caused an increase in congenital anomalies. A consistent pattern of congenital anomalies was not identified in human reports after typical exposures to aspirin. An increase in miscarriage risk after aspirin exposure around the time of conception has been proposed. NSAIDs including aspirin can cause premature closure of the ductus arteriosus when given in late pregnancy (after 30 weeks) and bleeding irregularities. These findings do not raise concerns when low dose (60-100 mg/day) aspirin is used."

A prospective cohort study of more than 50,000 mother-child pairs (the Collaborative Perinatal Project) assessing adverse outcomes by level of aspirin exposure did not report aspirin-induced teratogenicity, altered neonatal birth weight, or perinatal deaths at any exposure level.¹⁸ A retrospective, case-control study suggested that aspirin use during pregnancy might increase the risk of certain heart defects (defects in septation of the truncus arteriosus i.e. transposition of the great arteries, tetralogy of Fallot, and truncus arteriosus) in the offspring.¹⁹ However, other case-control studies of children with congenital heart defects found no association between these abnormalities and maternal use of aspirin during pregnancy.^{20,21} An increased incidence of post-term pregnancy and longer duration of pregnancy in women taking aspirin has been reported.²²

A multinational study involving more than 9,000 women, CLASP (Collaborative Low-dose Aspirin Study in Pregnancy)], found that low-dose aspirin reduced fetal morbidity in a select population of women with early-onset preeclampsia, but did not identify adverse effects in the pregnant woman, fetus, or newborn (followed to 12 and 18 months of age) in association with the use of low-dose aspirin during pregnancy.²³ In contrast, some case-control studies reported associations between human congenital malformations and aspirin use early in gestation, but these studies did not report a consistent outcome attributable to drug use.

¹⁷ Truven health Analytics-Micromedex Solutions

¹⁸ Slone D et al.: Aspirin and congenital malformations. *Lancet* 1:1373-5, 1976

¹⁹ Zierler S, Rothman KJ: Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. *N Engl J Med* 313:347-52, 1985

²⁰ Bateman DN, McElhatton PR, Dickinson D, Wren C, Matthews JN, O'Keeffe M, Thomas SH: A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England. *Eur J Clin Pharmacol* 60: 635-641, 2004

²¹ Marsh CA, Cragan JD, Alverson CJ, Correa A. 2014. Case-control analysis of maternal prenatal analgesic use and cardiovascular malformations: Baltimore-Washington Infant Study. *Am J Obstet Gynecol* 211(4): e1-e9. doi: 10.1016/j.ajog.2014.03.054

²² Lewis RB, Schulman JD: Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labor. *Lancet* 2:1159-1163, 1973

²³ CLASP collaborative group: Low dose aspirin in pregnancy and early childhood development: follow up of the collaborative low dose aspirin study in pregnancy. *Br J Obstet Gynaecol* 1995; 102:861-8

In a meta-analysis of randomized clinical trials, no effect of low-dose aspirin started prior to 17 weeks of gestation was observed on risk of pre-eclampsia, severe pre-eclampsia, or having a small for gestational age infant. No difference was observed between starting low-dose aspirin prior to or after 17 weeks gestation.²⁴ Another trial of 3294 pregnant women of 14 to 20 weeks of gestation treated with aspirin showed no effect in the mothers' incidence of pre-eclampsia, hypertension, HELLP syndrome or placental abruption, or in the incidence of perinatal deaths or low birth weight below the 10th percentile. The incidence of maternal side effects was higher in the aspirin group, principally because of a significantly higher rate of hemorrhage.²⁵ Another study showed aspirin administration was not associated with any excessive risk of infant or maternal bleeding. However, there were no significant differences between cases and controls in terms of the incidence of proteinuric pre-eclampsia, preterm delivery, birth weight under 1500 g, or stillbirth and neonatal death.²⁶ The trial by Sibai et. al. revealed that there were no significant differences in the infants' birth weight or in the incidence of fetal growth retardation, postpartum hemorrhage, or neonatal bleeding problems between the women who took aspirin versus placebo but the incidence of placenta abruption was greater among the women who received aspirin.²⁷

A 2014 report from the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, which evaluated 1078 women who were attempting to become pregnant and had prior miscarriages, addressed whether daily preconception-initiated treatment with low-dose aspirin improved the livebirth rate compared with placebo in women with one to two previous pregnancy losses.^{28,29} The study reported a significant increase in livebirth rate only among women with a history of a single pregnancy loss before 20 weeks gestation. No significant effect was found when women with multiple losses were included. The data were not sufficient to justify the use of low dose aspirin for the prevention of pregnancy loss. .

²⁴ Roberge S, Sibai B, McCaw-Binns A, Bujold E. 2016. Low-dose aspirin in early gestation for prevention of preeclampsia and small-for-gestational-age neonates: Meta-analysis of large randomized trials. *Am J Perinatol* doi: <http://dx.doi.org/10.1055/s-0036-1572495>

²⁵ Subtil D, Goeusse P, Puech F , et al; Essai Régional Aspirine Mère-Enfant (ERASME) Collaborative Group. Aspirin (100 mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Régional Aspirine Mère-Enfant study (Part 1).

²⁶ Rotchell YE, Cruickshank JK, Gay MP , et al. Barbados Low Dose Aspirin Study in Pregnancy (BLASP): a randomised trial for the prevention of pre-eclampsia and its complications. *Br J Obstet Gynaecol* 1998; 105 (3) 286-292

²⁷ Sibai BM, Caritis SN, Thom E , et al; The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. *N Engl J Med* 1993; 329 (17) 1213-1218

²⁸ Schisterman EF, Silver RM, Leshner LL, Faraggi D, Wactawski-Wende J, Townsend JM, Lynch AM, Perkins NJ, Mumford SL, Galai N. 2014. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet* 384(9937): 29-36. doi: 10.1016/S0140-6736(14)60157-4. PubMed PMID: 24702835.

²⁹ Schisterman EF, Mumford SL, Schliep KC, Sjaarda LA, Stanford JB, Leshner LL, Wactawski-Wende J, Lynch AM, Townsend JM, Perkins NJ, Zarek SM, Tsai MY, Chen Z, Faraggi D, Galai N, Silver RM. 2015. Preconception low dose aspirin and time to pregnancy: findings from the effects of aspirin in gestation and reproduction randomized trial. *J Clin Endocrinol Metab* 2015.100(5): 1785-1791.

Another multicenter, randomized, controlled trial found that women with prior miscarriages could use low-dose aspirin without adverse maternal or fetal side effects except for vaginal bleeding, which was more commonly reported in the aspirin group than in the placebo group.³⁰

Newborns exposed *in utero* to low dose aspirin did not have an excessive risk of bleeding abnormalities.^{31,32} Low doses of aspirin might permit normal hemostasis in the fetus and newborn.^{33,34}

In a prospective randomized controlled study of women in the third trimester of pregnancy treated until delivery with up to 80 mg/day of aspirin, neonatal levels of 6-keto-prostaglandin F1 alpha and thromboxane B2 were unaffected. Platelet aggregation was not inhibited, and all infants had normal echocardiograms, and no evidence of cephalohematoma, gastrointestinal bleeding, or purpura.³⁵ Another study, a randomized, prospective, control trial, confirmed that low-dose aspirin therapy during pregnancy did not increase neonatal bleeding complications.³⁶

Omeprazole

The clinical experience data on omeprazole and esomeprazole have been previously reviewed by DPMH and remain unchanged. For more details, the reader is referred to the prior DPMH reviews of Prilosec³⁷ and Vimovo³⁸ by Christos Mastroyannis, M.D.

As stated in a previous DPMH review³⁹ of “Prilosec and Pregnancy” for the Pregnancy and Nursing Mothers Labeling, an expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair). No new data related to safety concerns of omeprazole use during pregnancy have been published since the last DMPH review completed in January 2016.³⁰

³⁰ Ahrens KA, Silver RM, Mumford SL, Sjaarda LA, Perkins NJ, Wactawski-Wende, Galai N, Townsend JM, et al. 2016. Complications and safety of preconception low-dose aspirin among women with prior pregnancy losses. *Ob Gyn* 127(4): 689-698

³¹ Schiff E et al.: The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to prostacyclin in relatively high risk pregnancies. *N Engl J Med* 321:351-6, 1989

³² Trudinger BJ et al.: Low-dose aspirin therapy improves fetal weight in umbilical placental insufficiency. *Am J Obstet Gynecol* 159:681-5, 1988

³³ Benigni A et al.: Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. *N Engl J Med* 321:357-62, 1989

³⁴ Ylikorkala O et al.: Maternal ingestion of acetylsalicylic acid inhibits fetal and neonatal prostacyclin and thromboxane in humans. *Am J Obstet Gynecol* 155:345-9, 1986

³⁵ Sibai BM, Mirro R, Chesney CM, Leffler C: Low-dose aspirin in pregnancy. *Obstet Gynecol* 74:551-557, 1989

³⁶ Sibai BM, Caritis SN, Thom E et al.: Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. *N Engl J Med* 1993;329:1213-8.

³⁷ DPMH review. Prilosec (omeprazole magnesium) delayed-release oral suspension, NDA 022056. by Christos Mastroyannis, M.D. January 15, 2016. DARRTS Reference ID 3873309. of NDA 022056

³⁸ Vimovo (naproxen/esomeprazole) delayed-release tablets. NDA 22511/s-018. Christos Mastroyannis, M.D. March 2, 2016. DARRTS Reference ID 3900270.

³⁹ Best J., DPMH review DARRTS April 15, 2013

An Office of Surveillance and Epidemiology (OSE) review dated January 15, 2014⁴⁰, assessed ten published observational studies of PPIs to determine if there is sufficient evidence to justify the sponsor's changes to the labeling in regards to the risk of PPIs use in pregnancy and congenital malformations. OSE concluded that the results showed a statistically insignificant risk (see reviews in DARRTS by Carrie Ceresa of 11/8/2013⁴¹ and Robert Campbell of 1/15/2014). Further review of Cochrane Pregnancy and Childbirth Group's Trials Register (June 30, 2015³³), ClinicalTrials.gov (March 2, 2015), as well as a PubMed search using the terms "Prilosec or omeprazole or PPI" and "pregnancy" and searching for publications between 2013 to 2016 did not produce any additional publications.

Review of Pharmacovigilance Data

The sponsor did not include post-marketing pharmacovigilance data for this specific combination product because it is not yet approved.

Summary

Yosprala

There are no adequate and well-controlled studies with Yosprala in pregnant women. Starting at 30 weeks gestation, Yosprala, and other NSAID-containing products, should be avoided by pregnant women. Evidence suggests that NSAIDs, including aspirin, a component of Yosprala, may increase risk of neonatal complications, such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage with third trimester maternal use. Salicylate-containing products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

Aspirin

From the randomized controlled trials (RCTs) presented above regarding aspirin use during pregnancy, this reviewer concludes that:

1. In preeclampsia, low-dose aspirin reduces fetal morbidity in a select population of women with early-onset preeclampsia when associated with preexisting disorders, including chronic hypertension or renal disease, or those who developed preeclampsia before 32 weeks of gestation in a previous pregnancy with no significant adverse effects in mother, fetus, or newborn in association with the use of low-dose aspirin
2. A significant increase in livebirth rate only occurs among women with a history of a single pregnancy loss before 20 weeks gestation but there are no sufficient data to justify the use of low dose aspirin for the prevention of pregnancy loss.
3. With use of low-dose aspirin, adverse maternal or fetal adverse effects are not expected, except for vaginal bleeding.
4. Low-dose aspirin therapy during pregnancy does not increase neonatal bleeding complications.

⁴⁰ Cambell R. Epidemiology: Literature Review, DARRTS, January 15, 2014 Reference ID: 3435725

⁴¹ Ceresa, Carrie. DPMH Review in DARRTS, Novemebr 8, 2013 Reference ID: 3403670

There are clinical considerations for the Yosprala labeling,

1. Maternal: Aspirin, should be avoided one week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have also been reported with aspirin. In animal studies, NSAIDs, including aspirin, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.
2. Fetal/Neonatal Adverse Reactions: Maternal aspirin use during the third trimester of pregnancy may increase the risk of neonatal complications, including necrotizing enterocolitis, patent ductus arteriosus, intracranial hemorrhage in premature infants, low birth weight, stillbirth and neonatal death.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID). DAAAP has developed template labeling for NSAIDs which is derived from an extensive review of NSAIDs as class labeling. This template language is incorporated in this labeling review and Yosprala labeling.

LACTATION

Nonclinical Experience

There is no information about Yosprala and its presence in animal milk.

Review of Literature

No publications with use of Yosprala during lactation were identified.

Aspirin

The applicant performed a PubMed literature search in order to identify published literature regarding aspirin use in lactating women. Terms included “breastfeeding or lactation” and “aspirin”. The applicant identified the following publications:

A publication by Bloor, *et al.*,⁴² states that aspirin persists in maternal milk for up to 24 hours and neonatal metabolism is slow. Even after a single dose, once lactation is fully established, the infant is exposed to 9% to 21% of the maternal dose. Bailey *et. al.* studied a woman who took chronic therapeutic doses of aspirin. Salicylate concentrations were maximal in serum at 2.25 hours (10.8 mg/dL) and in milk at 3.00 hours (1.0 mg/dL) following 975 mg of aspirin. Milk/serum concentration ratios ranged up to 0.08. The authors concluded that the infant should consume more than 25 liters of milk at its peak drug concentration to provide the salicylate content of one aspirin tablet.⁴³ Toxic effects on breastfed infants exposed to larger doses of salicylates (2–4 g/d) have been known for a long time. Adverse effects of aspirin on neonatal platelet function are a theoretical risk that has not been studied. Bailey *et. al.*, determined the relative infant dose, with maternal ingestion of aspirin, will be 9.4% of the maternal dose.⁴⁴ The American Academy of Pediatrics classifies aspirin under drugs that “have been associated with significant effects on

⁴² Bloor M, Paech M. Nonsteroidal Anti-Inflammatory Drugs During Pregnancy and the Initiation of Lactation. *Anesthesia & Analgesia* 2013;116(5):1063–1075

⁴³ Bailey DN, Weibert RT, Naylor AJ, Shaw RF. A study of salicylate and caffeine excretion in the breast milk of two nursing mothers. *J Anal Toxicol*

⁴⁴ Bailey DN, Weibert RT, Naylor AJ, Shaw RF: A study of salicylate and caffeine excretion in the breast milk of two nursing mothers. *J Anal Toxicol* 6:64-8, 1982. 43

some nursing infants and should be given to nursing mothers with caution.” Because of the theoretical risk of the Reye’s syndrome, the British National Formulary states that it should be avoided when breastfeeding.⁴²

DPMH conducted a search of Medications and Mother’s Milk⁴⁵, the Drugs and Lactation Database (LactMed),⁴⁶ Micromedex,⁴⁷ and of published literature in PubMed using the search terms “aspirin and lactation” and “aspirin and breastfeeding.” A review of literature is included below

The Drugs and Lactation Database (LactMed) was searched for available lactation data on with the use of aspirin. The Summary of Use during Lactation notes the following:

“Aspirin is best avoided during breastfeeding; however, some expert opinion indicates that low-dose (75-162 mg daily) aspirin may be considered as an antiplatelet drug for use in breastfeeding women. If low-dose aspirin is taken, avoiding breastfeeding for 1 to 2 hours after a dose might minimize the risks of antiplatelet effects in the infant. Long-term, high-dose maternal aspirin ingestion probably caused metabolic acidosis in one breastfed infant. Reye’s syndrome is associated with aspirin administration to infants with viral infections... An alternate drug is preferred over continuous high-dose, aspirin therapy.”

As per Bloor et.al, the NSAIDs are acidic drugs (e.g., ketorolac pKa 3.5 and indomethacin 4.5) with low lipid solubility and high protein binding (>90%), features that mitigate against substantial transfer into breastmilk, which is slightly acidic (mean pH 7.1–7.2) compared with plasma. The latter characteristic also favors drug transfer of the non-ionized form back from the milk to more alkaline maternal plasma (reverse “ion-trapping”) and thus milk to plasma ratios of NSAIDs are generally <14.⁴² Micromedex reports that aspirin and other salicylates are transferred into human milk.^{48,49,50,51}

In one case report, metabolic acidosis developed in the infant of a women who ingested a salicylate daily while breastfeeding.⁵²

⁴⁵ Hale, Thomas (2012) Medications and Mothers’ Milk. Amarillo, Texas Hale Publishing, 2012

⁴⁶ United States National Library of Medicine. TOXNET Toxicology Data Network. Drugs and Lactation Database (LactMed). <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding

⁴⁷ Truven Health Analytics information, <http://www.micromedexsolutions.com/>.

⁴⁸ Jamali F, Keshavarz E: Salicylate in breast milk. *Int J Pharm* 8:285-290, 1981

⁴⁹ Levy G: Salicylate pharmacokinetics in the human neonate. In: Morselli PL, Garattini S, Sereni F (eds) *Basic and Therapeutic Aspects of Perinatal Pharmacology*, Raven Press, NY. 1975. pp. 319-29

⁵⁰ Findlay JWA, DeAngelis RL, Kearney MF, Welch RM, Findlay JM: Analgesic drugs breast milk and plasma. *Clin Pharmacol Ther* 29:625-33, 1981

⁵¹ Bailey DN, Weibert RT, Naylor AJ, Shaw RF: A study of salicylate and caffeine excretion in the breast milk of two nursing mothers. *J Anal Toxicol* 6:64-8, 1982

⁵² Clark JH, Wilson WG: A 16-day-old breast-fed infant with metabolic acidosis caused by salicylate. *Clin Pediatr (Phila)*. 1981;20(1):53-4

Experimental animal and human data suggested that the reduced clearance of salicylates by neonates might result in drug accumulation and toxic effects even when repeated exposures are small.⁵³ Because of these concerns, the WHO Working Group on Human Lactation classified the salicylates as unsafe for use by nursing women.⁵⁴ In Britain, the use of aspirin during breastfeeding was categorized as contraindicated due to a theoretical risk of Reye Syndrome.⁵⁵

Medications and Mothers' Milk by Thomas Hale, a breastfeeding expert, was also reviewed. Dr. Hale reports that "extremely small amounts are secreted into breast milk and few harmful effects have been reported." Dr. Hale also reviewed several lactation studies. In one study with a dose of 454 mg of aspirin, peak levels in milk was 1.12 to 1.6mcg/ml, whereas maternal peak plasma levels were 33 to 43.4 mcg/ml.³⁸ In a lactation study of eight women, who received a 1 gram oral dose of aspirin, the average milk levels were 2.4 mcg/ml. The authors suggest that the relative infant dose would be 9.4% of the maternal dose.⁵⁶ Dr. Hale also states the following:

"While the direct use of aspirin in infants and children is definitely implicated in Reye syndrome, the use of 82 mg/day dose of aspirin in breastfeeding mothers is unlikely to increase the risk of this syndrome. Unfortunately we do not at present know of any dose-dependent relationship between Reye syndrome other than in older children where even low plasma levels of aspirin were implicated in Reye syndrome. Therefore, the use of aspirin in breastfeeding mothers is questionable, but the risk is probably low. Consider ibuprofen and acetaminophen as better choices for pain relief in lactating women."

Omeprazole

Data on omeprazole and esomeprazole in pregnancy have been previously reviewed and remain unchanged. There is only one case report of a breastfeeding mother who took omeprazole 20mg. Omeprazole was measured in the mother's milk at three weeks postpartum, and the authors calculated the relative infant dose to be 0.9% of the maternal weight-adjusted dosage. The infant was reported to be well at 12 months of age.⁵⁷ For more details, the reader is referred to the prior DPMH review of Prilosec by Christos Mastroyannis, M.D.³ and current Prilosec labeling in Drugs@FDA. No further review of omeprazole was conducted.

Summary

There is no information about the presence of Yosprala in human milk; however, published data have demonstrated the presence of both aspirin and omeprazole in human milk when taken as single agents.

⁵³ McNamara PJ, Burgio D, Yoo SD: Pharmacokinetics of acetaminophen, antipyrine, and salicylic acid in the lactating and nursing rabbit, with model predictions of milk to serum concentration ratios and neonatal dose. *Toxicol Appl Pharmacol* 109:149-60, 1991

⁵⁴ The WHO Working Group, Bennet PN (ed): *Drugs and Human Lactation*. Elsevier, Amsterdam, New York, Oxford, 1988. pp. 325-6.

⁵⁵ British National Formulary, September 1992, Appendix 5, Prescribing in Breast Feeding

⁵⁶ Putter J, Satravaha P, Stockhausen H. Quantitative analysis of the main metabolites of acetylsalicylic acid. Comparative analysis in the blood and milk of lactating women. *Z Geburtshilfe Perinatol.* 1974;178:135-8

⁵⁷ Marshall JK, Thompson AB, Armstrong D. Omeprazole for refractory gastroesophageal reflux disease during pregnancy and lactation. *Can J Gastroenterol.* 1998;12:225-7

Aspirin

Aspirin is present in breast milk and harmful effects (metabolic acidosis⁵⁸, thrombocytopenia⁵⁹ and hemolysis⁶⁰) have been reported in three case reports. The relative infant dose has been calculated to be 9.4%, on average, (2.5-10.8% per Dr. Hale) of the maternal dose. While direct use of aspirin in infants and children is implicated in Reye syndrome, the use of 82 mg/day dose of aspirin in breastfeeding mothers is unlikely to increase the risk of this syndrome. However, since we do not know what the dose-dependent relationship is between aspirin exposure in an infant and Reye syndrome, DPMH agrees with applicant that breastfeeding is not recommended with use of Yosprala.

Omeprazole

Limited data from one case report suggests omeprazole may be present in human milk in low levels. There is no information on the effects of omeprazole on the breastfed infant or on milk production.

Reviewer comment

This reviewer concludes that because of the potential for serious adverse reactions, including the potential for aspirin to cause metabolic acidosis, thrombocytopenia, hemolysis or Reye's syndrome, patients should be advised that breastfeeding is not recommended during treatment with YOSPRALA.

Females and Males of Reproductive Potential

Nonclinical Experience

No animal fertility studies were conducted with Yosprala.

Aspirin

Rat and rabbit studies reported ovulation inhibition in association with aspirin and other prostaglandin inhibitors.^{61,62,63}

Review of Literature

Aspirin

Aspirin and other NSAIDs might play a role in at least one type of female infertility. Prostaglandin inhibition increased the incidence of luteinized unruptured follicle syndrome, a condition in which normal ovarian follicular development was followed by an elevation of serum

⁵⁸ Clark JH, Wilson WG. A 16-day-old breast-fed infant with metabolic acidosis caused by salicylate. Clin Pediatr. 1981;20:53-4.

⁵⁹ Terragna A, Spirito L. [Thrombocytopenic purpura in an infant after administration of acetylsalicylic acid to the wet-nurse]. Minerva Pediatr. 1967;19:613-6.

⁶⁰ Arley JD, Robin H. "Late" neonatal jaundice in infants with glucose-6-phosphate dehydrogenase-deficient erythrocytes.

⁶¹ Zanagnolo V, Dharmarajan AM, Endo K, Wallach EE. Effects of acetylsalicylic acid (aspirin) and naproxen sodium (naproxen) on ovulation, prostaglandin, and progesterone production in the rabbit. Fertil Steril 1996;65:1036-43.

⁶² Armstrong DT, Greenwich DL: Blockade of spontaneous and LH-induced ovulation in rats by indomethacin, an inhibitor of prostaglandin synthesis. Prostaglandins 1972;1:21.

⁶³ O'Grady JP, Caldwell BV, Auletta FJ, Speroff L: The effects of an inhibitor of prostaglandin synthesis (indomethacin) on ovulation, pregnancy and pseudo-pregnancy in the rabbit. Prostaglandins 1972;1:97

progesterone compatible with ovulation, but the cycle remained anovulatory because the follicular wall remained unruptured.^{64,65} In women, ultrasound scans of follicular development showed a fivefold increase in the incidence of this syndrome in the presence of some NSAIDs.⁵⁰ The prolonged use of NSAIDs was most likely to be associated with this antifertility effect.

In contrast to this observation, one group of investigators reported that low-dose aspirin (100 mg/day) improved implantation and pregnancy rates in patients undergoing in vitro fertilization.⁶⁶ They hypothesize that this effect might be mediated by improved ovarian and uterine blood flow associated with this low dose of aspirin. Two studies that primarily involved NSAIDs other than aspirin reported a possible increased risk of miscarriage when these agents have been taken around the time of conception or for more than a week.^{67,68}

Omeprazole

There are no human data available regarding the effects of Prilosec on fertility.

Summary

Pregnancy Testing and Contraception

Based on the above review, the available human data do not support a clear conclusion on an increased risk of major congenital malformations. Therefore, no labeling recommendations for pregnancy testing or contraception use are suggested for the Yosprala labeling.

Infertility

Aspirin and other NSAIDs may increase the incidence of luteinized unruptured follicle syndrome, a condition in which normal ovarian follicular development is followed by an elevation of serum progesterone compatible with ovulation, but the cycle remains anovulatory because the follicular wall remained unruptured. Labeling will be structured to comply with the NSAID labeling template and will state the following:

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

⁶⁴ Marik J, Hulka J: Luteinized unruptured follicle syndrome: a subtle cause of infertility. *Fertil Steril* 1978;29:270.

⁶⁵ Killick S, Elstein M: Pharmacological production of luteinized unruptured follicles by prostaglandin synthetase inhibitors. *Fertil Steril* 1987;47:773-7.

⁶⁶ Rubinstein M, Marazzi A, Polak de Fried E: Low-dose aspirin treatment improves ovarian responsiveness, uterine and ovarian blood flow velocity, implantation, and pregnancy rates in patients undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled assay. *Fertil Steril* 1999;71:825-9

⁶⁷ Nielsen GL, Sorensen HT, Larsen H, Pedersen L: Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal antiinflammatory drugs; population based observational study and case-control study. *BMJ* 322:266-70, 2001

⁶⁸ Li D-K, Liu L, Odouli R: Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003;327:368-70

NSAIDs, including YOSPRALA, in women who have difficulties conceiving or who are undergoing investigation of infertility.

CONCLUSION

The Pregnancy and Lactation sections of Yosprala labeling were structured to be consistent with the PLLR as follows:

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

RECOMMENDATIONS

DPMH participated in a labeling meeting with DGIEP. DPMH revised sections 8.1, 8.2, 8.3 and 17 of Yosprala labeling for compliance with the PLLR and with the NSAID labeling template. DPMH refers to the final NDA action for final labeling. DPMH proposed labeling for Yosprala is included in Appendix A.

**APPENDIX A:
DPMH PROPOSED PREGNANCY AND LACTATION LABELING EDITS FOR
YOSPRALA**

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

Premature closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation. (5.18, 8.1)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.18, 8.1)
- Lactation: Breastfeeding not recommended. (8.2)
- Females and Males of Reproductive Potential: NSAIDs are associated with reversible infertility. Consider withdrawal of YOSPRALA in women who have difficulties conceiving. (8.3)

FULL PRESCRIBING INFORMATION: CONTENTS

5 WARNINGS AND PRECAUTIONS

5.18 Premature Closure of the Fetal Ductus Arteriosus

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.18 Premature Closure of Fetal Ductus Arteriosus

NSAIDs, including aspirin, may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including YOSPRALA, in pregnant women starting at 30 weeks of gestation (third trimester). Maternal aspirin use during later stages of pregnancy may cause low birth weight, increased incidence for intracranial hemorrhage in premature infants, stillbirths and neonatal death [see *Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

and miscarriage; however, there are published studies with each individual component of YOSPRALA.

Aspirin

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

Omeprazole

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

Changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole [see *Data*].

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Maternal aspirin use during the third trimester of pregnancy may increase the risk of neonatal complications, including necrotizing enterocolitis, patent ductus arteriosus, intracranial hemorrhage in premature infants, low birth weight, stillbirth and neonatal death. Avoid use of NSAIDs, including YOSPRALA, in pregnant women in the third trimester.

Maternal Adverse Reactions

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

Labor or Delivery

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

Data

Human Data

Aspirin

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

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

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

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

Omeprazole

Four published epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls.

A population-based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995 to 1999, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number

of infants exposed in utero to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

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

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H2-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

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

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

Animal Data

Aspirin

Aspirin produced a spectrum of developmental anomalies when administered to Wistar rats as single, large doses (500 to 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 doses 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 40 mg 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 40 mg 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 40 mg 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 40 mg 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 hypo-cellularity 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 40 mg 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 40 mg 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 40 mg 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 40 mg 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.

8.2 Lactation

Risk Summary

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

Clinical Considerations

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

8.3 Females and Males of Reproductive Potential Infertility

Infertility

Females

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

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

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

Lactation

Advise women that breastfeeding is not recommended during treatment with YOSPRALA [*see Use in Specific Populations (8.2)*].

Infertility

Advise females of reproductive potential that NSAIDs, including YOSPRALA, may be associated with reversible infertility [*see Use in Specific Populations (8.3)*].

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/s/

CHRISTOS MASTROYANNIS
08/25/2016

TAMARA N JOHNSON
08/29/2016

LYNNE P YAO
08/29/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health Staff
Office of New Drugs

Through: Donna Snyder, M.D., Acting Pediatrics Team Leader
John Alexander, M.D., M.P.H., Deputy Director
Division of Pediatric and Maternal Health Staff
Office of New Drugs

To: Division of Gastroenterology and Inborn Errors Products
(DGIEP)

Drug: Yosprala® (aspirin/omeprazole)
Two proposed dosages in tablet formulation:
-81 mg delayed release aspirin/40 mg immediate release
omeprazole or
-325 mg delayed release aspirin/40 mg immediate release
omeprazole

Application number: NDA 205103

Re: Labeling Review for Pediatric Use

Sponsor: Pozen, Inc.

Proposed Indication: (b) (4)

Consult request:

DGIEP requests DPMH's review of labeling for this application.

Materials Reviewed:

- DPMH Consult Request (May 11, 2016)
- Applicant's proposed labeling (March 14, 2016)
- Previous DPMH review for Yosprala (aspirin/omeprazole), NDA 205103 by Donna Snyder, M.D. (December 22, 2013)

Background:

Pozen, Inc. originally submitted the application for Yosprala (aspirin/omeprazole) delayed-release tablets, 81 mg/40 mg and 325 mg/40mg, 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. This application was issued two Complete Responses over the course of the review related to manufacturing facility inspection deficiencies and labeling deficiencies. On March 14, 2016, Pozen, Inc. resubmitted their application, and DGIEP requested DPMH's assistance with the review of the labeling. The DPMH-Pediatric team's current review focused on sections 4 (Contraindications) and 8.4 (Pediatric Use). The recommendations for pregnancy and lactation are provided in a separate review by the DPMH-Maternal Health team.

DPMH Actions and Labeling Recommendations:

DPMH's labeling recommendations have remained unchanged except for subsection 8.4. Based on collaboration with the division, the language describing the contraindication in pediatric patients was modified to provide more clarity regarding the reason for the contraindication similar to the language included in the Contraindications section. Additionally, a heading was included for the juvenile animal data.

DPMH reviewed the sponsor's draft labeling and participated in the internal meetings from June, 2016 to August, 2016. Recommended labeling for the pediatric population based on labeling discussions between DGIEP and DPMH is provided per 21 CFR 201.57(c)(9)(iv) below. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested in this review.

PMHS-PEDIATRIC TEAM RECOMMENDATIONS FOR LABELING:

4 CONTRAINDICATIONS

YOSPRALA is contraindicated in:

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

8.4 Pediatric Use

The safety and efficacy of YOSPRALA has not been established in pediatric patients. (b) (4)

YOSPRALA is contraindicated in pediatric patients with suspected viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses [see Contraindications (4)].

Juvenile Animal Data

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about (b) (4) 17 to (b) (4) 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)].

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/s/

ERICA D RADDEN
08/12/2016

DONNA L SNYDER
08/12/2016

JOHN J ALEXANDER
08/12/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 11, 2016

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): YOSPRALA (aspirin and omeprazole)

Dosage Form and Route: delayed-release tablets, for oral use

Application Type/Number: NDA 205103

Applicant: Pozen, Inc.

1 INTRODUCTION

On March 14, 2016, Pozen, Inc. re-submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 205103 for YOSPRALA (aspirin and omeprazole) delayed-release tablets. The Division of Gastroenterology and Inborn Errors Products (DGIEP) considers the Applicant's submission to be a complete, class 2 response to the Agency's Complete Response Letter issued on December 16, 2014. The Agency issued a prior Complete Response Letter to Pozen, Inc. for this NDA on April 25, 2014. The proposed indication for YOSPRALA (aspirin and omeprazole) delayed-release tablets is for use in patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcer.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on May 13, 2016, and August 4, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for YOSPRALA (aspirin and omeprazole) delayed-release tablets.

2 MATERIAL REVIEWED

- Draft YOSPRALA (aspirin and omeprazole) delayed-release tablets MG received on June 1, 2016 and received by DMPP and OPDP on August 3, 2016.
- Draft YOSPRALA (aspirin and omeprazole) delayed-release tablets Prescribing Information (PI) received on June 1, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 8, 2016.
- Approved PRILOSEC (omeprazole) delayed-release capsules comparator labeling dated February 3, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
08/11/2016

MEETA N PATEL
08/11/2016

LASHAWN M GRIFFITHS
08/11/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 8, 2016

To: Mimi Phan, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205103
OPDP Comments for draft Yosprala (aspirin and omeprazole) delayed
release tablets, PI and PPI

OPDP has reviewed the proposed draft Yosprala (aspirin and omeprazole) delayed release tablets Prescribing Information (PI). We have reviewed the draft PI, retrieved from SharePoint on August 8, 2016, and have no additional comments. The PPI will be reviewed jointly with DMPP and sent under a separate cover.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
08/08/2016

MEMORANDUM

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

DATE: 8/3/2016

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 205103

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. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	PPD Phase 1 Clinic	7551 Metro Center Drive, Suite 200, Austin, TX

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/s/

SHILA S NKAH
08/08/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: July 28, 2016

Requesting Office or Division: Division of Gastroenterology and Inborn Error Products (DGIEP)

Application Type and Number: NDA 205103

Product Name and Strength: Yosprala (Aspirin and Omeprazole)
Delayed-release Tablets
325 mg/40 mg and 81 mg/40 mg

Submission Date: March 14, 2016

Applicant/Sponsor Name: Aralez Pharmaceuticals

OSE RCM #: 2016-1930

DMEPA Primary Reviewer: Sherly Abraham, R.Ph.

DMEPA Team Leader: Mishale Mistry, Pharm.D., MPH

1 REASON FOR REVIEW

This review evaluates the proposed container labels and prescribing information labeling for Yosprala (aspirin and omeprazole), NDA 205103, submitted on March 14, 2016. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the labels and labeling for areas of vulnerability related to medication errors.

1.1 BACKGROUND

Pozen submitted a 505(b)(2) NDA for Yosprala (aspirin and omeprazole) on March 25, 2013. As part of the review of the application, DMEPA reviewed the proposed labels and labeling for Yosprala, and on March 29, 2014, DMEPA's recommendations were communicated to the sponsor.¹ On April 25, 2014, the application received a Complete Response (CR) due to manufacturing facility deficiencies. Pozen resubmitted the application on June 30, 2014 and provided revised label and labeling on July 28, 2014. The application received a second Complete Response on December 16, 2014 due to unresolved issues involving manufacturing facility deficiencies. On March 14, 2016, Pozen resubmitted the application for review in response to the CR; the revised carton labeling and container labels were submitted on June 1, 2016, to reflect the change in corporate name of the sponsor from Pozen to Aralez Pharmaceuticals.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)	E-N/A

¹Khosla, L. Label and Labeling Review for Yosprala (NDA 205103). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 12 3. 32 p. OSE RCM No.: 2013-993.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed labels and labeling to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. Although we found the prescribing information acceptable, we note that the labels and labeling can be improved to increase readability and prominence of important information. Specifically, we identified that the proprietary name is printed in gray font, which does not afford adequate contrast against the white background. Additionally, there is not adequate space between the strength and unit of measure. We provide the recommendations for the Applicant in Section 4.1 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product.

4.1 RECOMMENDATIONS TO ARALEZ PHARMACEUTICALS

A. Container Labels:

1. As currently presented, the proprietary name is difficult to read [redacted] (b) (4) [redacted] We recommend that you increase the prominence of the proprietary name to improve readability.
2. We recommend that you include a space between the numerical strength and unit of measure (e.g. 81 mg/40 mg vs. 81mg/40mg) as the letter “m” can be confused for a zero or two zeros.
3. Consider combining the two dosage statements on the left and right of the principal display panel to the following statement: “Usual dose: Take 1 tablet daily at least 60 minutes before a meal. Tablet should be swallowed whole with liquid.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Yosprala that submitted by Aralez Pharmaceuticals by March 14, 2016.

Table 2. Relevant Product Information for Yosprala tablets	
Initial Approval Date	N/A
Active Ingredients	Aspirin and Omeprazole
Indication	<p>Yosprala 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 ulcers.</p> <p>The aspirin component of YOSPRALA is indicated for:</p> <ul style="list-style-type: none"> • reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, • reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, • reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, • use in patients who have undergone revascularization procedures (Coronary Artery Bypass Graft [CABG] or Percutaneous Transluminal Coronary Angioplasty [PTCA]) when there is a pre-existing condition for which aspirin is already indicated.
Route of Administration	oral
Dosage Form	Delayed-release tablets
Strength	81 mg delayed release aspirin/40 mg immediate release omeprazole and 325 mg delayed release aspirin/40 mg immediate release omeprazole
Dose and Frequency	One tablet once daily at least 60 minutes before a meal
How Supplied	Bottles of 30, 90 (b) (4) tablets
Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 27, 2016, we searched the L: drive and AIMS using the terms, Yosprala, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews², and we confirmed that our previous recommendations were implemented.

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

²Abraham, S. Label and Labeling Review Memo for Yosprala (NDA 205103). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 10 8. 32 p. OSE RCM No.: 2014-1930.

Khosla, L. Label and Labeling Review for Yosprala (NDA 205103). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 12 3. 32 p. OSE RCM No.: 2013-993.

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/s/

SHERLY ABRAHAM
07/28/2016

MISHALE P MISTRY
07/28/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Epidemiology: Review of a Research Article**

Date: July 11, 2016

Reviewer(s): Joel L. Weissfeld, MD MPH
Division of Epidemiology I

(Acting) Deputy Director: Simone P. Pinheiro, ScD MSc
Division of Epidemiology I

Drug Name(s): Yosprala (aspirin/omeprazole) tablets

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

Application Type/Number: NDA 205103

Applicant/sponsor: Pozen Incorporated

OSE RCM #: 2016-1448

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EXECUTIVE SUMMARY

To guide regulatory actions on a new drug application (NDA) for an aspirin -omeprazole combination product, the Division of Gastroenterology and Inborn Error Products (DGIEP) asked the Division of Epidemiology I (DEPI) to review a recently published scientific article about gastrointestinal (GI) bleeding risks from proton pump inhibitors (PPI) in patients on low-dose aspirin.

For older and chronically ill patients, practice guidelines recommend PPI to protect against GI complications from low-dose aspirin. In March 2016, Pozen Incorporated resubmitted NDA 205103 for Yosprala, a delayed-release tablet containing aspirin and the PPI omeprazole. A scientific article published by Miyake, et al., 2015, described an excess lower GI bleeding risk from PPI in patients on low-dose aspirin. (b) (4)

Miyake used medical records to construct three cohorts of patients (mean age 67.4 years) discharged on low-dose aspirin from a Japanese academic hospital after coronary angiography. After three years follow-up, Miyake documented lower GI bleeding in 9 of 107 (8.4%), 5 of 173 (2.9%), and 4 of 258 (1.6%) patients discharged on PPI, histamine-2 receptor antagonists (H2RA), and neither PPI nor H2RA, respectively. A Cox regression estimated lower GI bleeding risk from PPI use vs. PPI or H2RA nonuse at adjusted hazard ratio 6.55, 95% confidence interval 2.01-12.32.

DEPI found in Miyake serious risk of bias, with major concerns in two domains, confounding control and outcome measurement. Either source for concern could plausibly explain an artificial association in Miyake between PPI and lower GI bleeding in patients on low-dose aspirin. Also, DEPI found only weak evidence to support PPI as the causal explanation for the excess lower GI bleeding risk observed by Miyake. Serious risks of bias and weak evidence for causality severely limited the usefulness of results in Miyake.

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

1. INTRODUCTION

To guide regulatory actions on a new drug application (NDA) for an aspirin -omeprazole combination product, the Division of Gastroenterology and Inborn Error Products (DGIEP) asked the Division of Epidemiology I (DEPI) to review a recently published scientific article about gastrointestinal (GI) bleeding risks from proton pump inhibitors (PPI) in patients on low-dose aspirin.

For older and chronically ill patients, practice guidelines recommend PPI to protect against GI complications from low-dose aspirin (Lanza, et al., 2009). In March 2016, Pozen Incorporated resubmitted NDA 205103 for Yosprala, a delayed-release tablet containing aspirin and the PPI omeprazole.

From observation of patients discharged from a Japanese hospital after coronary catheterization, Miyake, et al., 2015, described an excess lower GI bleeding risk from PPI in patients on low-dose aspirin. (b) (4)

1.2. Regulatory History

Relevant regulatory events include:

Date	Event
March 14, 2016	Pozen Inc. resubmits NDA 205103 (eCTD 0042) for Yosprala, a delayed-release tablet containing aspirin 81 or 325 mg and omeprazole 40 mg

2. REVIEW METHODS AND MATERIALS

DEPI used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI; Sterne, et al., 2014) to guide its risk-of-bias assessment of Miyake, et al., 2015. The ACROBAT-NSRI conceives seven categories of risk to the internal validity of observational studies, (1) confounding, (2) selection, (3) measuring the intervention, (4) co-intervention, (5) missing data, (6) measuring the outcome, and (7) selective reporting.

DEPI used the 20-item scheme proposed by Elwood, 1998, to guide its assessment for causation.

3. REVIEW RESULTS

3.1 Study Overview

Miyake used medical records and a cohort design to study the association between gastric acid suppression and subsequent gastrointestinal (GI) bleeding in patients discharged on aspirin after coronary angiography at one hospital.

3.2 Objectives: Primary and Secondary

Miyake aimed to measure upper and lower GI bleeding risks from proton pump inhibition (PPI) or histamine-2 receptor antagonism (H2RA) in patients on low-dose aspirin.

3.3 Study Design

Miyake used a retrospective cohort study design.

3.4 Methods

3.4.1 Population sources and study time period

Miyake studied coronary angiography patients, discharged between October 2005 and December 2006, from the Nippon Medical School Hospital in Tokyo, Japan.

3.4.2 Study subject selection

Miyake enrolled consecutive coronary angiography patients discharged on low-dose aspirin (81–200 mg/day). Miyake excluded patients (1) treated with coronary artery bypass grafting or (2) not followed by physicians at the Nippon Medical School Hospital.

3.4.3 IRB/OMB approval, patient consent if needed.

Miyake followed “human and ethical principles in the Declaration of Helsinki.”

3.4.4 Exposure

By review of hospital records, Miyake defined exposure by hospital discharge on PPI or H2RA as concomitant medication to low-dose aspirin.

3.4.5 Outcome

Miyake ascertained outcomes by review of medical records for up to three years after hospital discharge. The outcome definition required,

- Clinical evidence for blood loss, defined by hematemesis, melena, bloody stool, hemoglobin drop ≥ 1.5 g/dL, or anemia (hemoglobin < 14 g/dL in men and < 12 g/dL in women).
- Endoscopic evidence for GI source, (1) ≥ 3 mm ulcer with mucosal break, (2) vascular lesion with blood clot or active bleeding, or (3) tumor > 1 cm in diameter.

Miyake used results from upper and lower GI endoscopy (esophagogastroduodenoscopy and colonoscopy, respectively) to distinguish upper from lower GI bleeding.

Two blinded and experienced physicians reviewed digital images from endoscopies and agreed on study outcomes.

3.4.6 Analysis plan

With follow-up censored at hospitalization or discontinuation of aspirin, Miyake used Cox proportional hazards regression to estimate GI bleeding risks (hazard ratio, HR). Multiple variable Cox regressions adjusted for other variables associated singly with study outcome at two-sided $p < 0.10$. Variables assessed at cohort entry and considered for statistical adjustment included,

- Demographic and behavioral factors of age, advanced age (≥ 70 years), male sex, obesity (body mass index ≥ 25 kg/m²), and smoking.
- Clinical factors of peptic ulcer history, renal dysfunction (creatinine ≥ 1.3 mg/dL), ejection fraction $< 40\%$, and triple vessel disease.
- Comorbidities of diabetes mellitus, hypertension, hyperlipidemia, and hyperuricemia.
- Concomitant use of antithrombotics (warfarin, ticlopidine, clopidogrel, or cilostazol),

calcium channel blockers, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, beta-blockers, HMG-CoA reductase inhibitors (statins), insulin, sulfonylurea, α -glucosidase inhibitors, and pioglitazone.

3.5 Results

3.5.1 Baseline characteristics

Miyake followed N=538 coronary angiography patients (74.4% men, mean age 67.4 ± 10.6 years), all discharged on low-dose aspirin, including 107 (19.9%), 173 (32.2%), and 258 (47.9%) discharged on PPI, H2RA, and neither PPI nor H2RA, respectively.

3.5.2 Other covariates

Table 1 shows other covariate results reported by Miyake in an online-only supplementary table. As shown in Table 1, DEPI calculated standardized covariate differences to guide comparisons between exposed and non-exposed groups.

Table 1: Proton pump inhibitor (PPI) users, histamine-2 receptor antagonist users, and control nonusers, number and percent, by other covariate characteristic, with difference between users and nonusers expressed as standardized difference (SD).[1]

Other covariate characteristic	Control N=258		PPI N=107			H2RA N=173		
	N	%	N	%	SD	N	%	SD
Demographic and behavioral								
age ≥ 70 years	102	39.5	56	52.3	0.26	73	42.2	0.05
male	188	72.9	79	73.8	0.02	133	76.9	0.09
obesity	97	37.6	38	35.5	-0.04	58	33.5	-0.09
smoking	163	63.2	68	63.6	0.01	119	68.8	0.12
Clinical								
peptic ulcer history	17	6.6	11	10.3	0.13	11	6.4	-0.01
renal dysfunction	36	14.0	23	21.5	0.20	27	15.6	0.05
low ejection fraction	36	14.0	28	26.2	0.31	27	15.6	0.05
triple vessel disease	36	14.0	27	25.2	0.29	23	13.3	-0.02
Comorbidity								
diabetes mellitus	112	43.4	51	47.7	0.09	70	40.5	-0.06
hypertension	172	66.7	80	74.8	0.18	126	72.8	0.13
hyperlipidemia	163	63.2	66	61.7	-0.03	111	64.2	0.02
hyperuricemia [2]	66	25.6	37	34.6	0.20	50	28.9	0.07
Concomitant medication								
multiple antithrombotics	178	69.0	72	67.3	-0.04	125	72.3	0.07
ticlopidine or clopidogrel	146	56.6	56	52.3	-0.09	95	54.9	-0.03
cilostazol	28	10.9	14	13.1	0.07	30	17.3	0.19
warfarin	8	3.1	3	2.8	-0.02	2	1.2	-0.14
calcium channel blocker	101	39.1	52	48.6	0.19	76	43.9	0.10

Other covariate characteristic	Control N=258		PPI N=107			H2RA N=173		
	N	%	N	%	SD	N	%	SD
angiotensin receptor blocker	142	55.0	67	62.6	0.15	95	54.9	0.00
ACE inhibitor [3]	24	9.3	8	7.5	-0.07	19	11.0	0.06
beta-blocker	196	76.0	83	77.6	0.04	138	79.8	0.09
statins	138	53.5	52	48.6	-0.10	105	60.7	0.15
insulin	20	7.8	9	8.4	0.02	16	9.2	0.05
sulfonylurea	39	15.1	18	16.8	0.05	24	13.9	-0.04
α -glucosidase inhibitor	20	7.8	17	15.9	0.25	20	11.6	0.13

1. Standardized difference, calculated by DEPI, as the standardized difference, according to Austin, PC, 2009, Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples, Stat Med, 28:3083-3107. Yellow highlights show standardized differences >0.10 in absolute value.
2. To resolve an inconsistency in Miyake, DEPI recalculated the percentage for H2RA from the count reported by Miyake.
3. Angiotensin-converting enzyme inhibitor.

3.5.3 Unadjusted results

With \approx 83-85% successful follow-up through three years, regardless of exposure grouping, Miyake ascertained 25 upper GI bleeding events (17 peptic ulcer, 6 gastric cancer, 1 esophagitis, and 1 esophageal ulcer) and 18 lower GI bleeding events (5 colon cancer, 3 diverticulum, 3 rectal ulcer, 2 ulcerative colitis, 2 hemorrhoids, 1 ischemic colitis, and 2 ileal ulcer). One patient had both upper and lower GI bleeding (peptic and ileal ulcers). Table 2 shows the frequency of outcome events according to exposure grouping.

Table 2: Bleeding events, by gastrointestinal (GI) source, according to exposure group, proton pump inhibitor (PPI) users, histamine-2 receptor antagonist users, and control nonusers.

Source	Control N=258	PPI N=107	H2RA N=173	ALL N=538
Lower GI N [1]	4	9	5	18
%	1.6	8.4	2.9	3.3
p-value [2]		0.001	\geq 0.05	
Upper GI N [1]	19	2	3	24
%	7.4	1.9	1.7	4.5
p-value [2]		0.062	0.011	

1. Patient with bleeding from both sources counted once in lower GI bleeding group.
2. p-value, statistical significance from log-rank test, with control group as reference.

3.5.4 Primary results

Controlled for hyperuricemia and warfarin use, one Cox regression model showed increased lower GI bleeding risks from PPI (HR 6.55, 95% confidence interval, CI, 2.01-12.32, p-value 0.002) and from H2RA (HR 1.96, 95% CI 0.52-7.31, p-value 0.32). Controlled for statin and calcium channel blocker use, a second Cox regression model showed decreased upper GI bleeding risks from PPI (HR 0.27, 95% CI 0.06-1.18, p-value 0.081) and from H2RA (HR 0.26,

95% CI 0.08-0.89, p-value 0.032).

3.6 Strengths and Limitations

Miyake mentioned simultaneous study of upper and lower GI bleeding as a study strength and retrospective data collection and lack of control for *Helicobacter pylori* infection as study limitations.

3.7 Conclusions

Miyake concluded that proton pump inhibitor use concomitant with aspirin increased lower GI bleeding risk.

4. DISCUSSION

Miyake used medical records to construct three cohorts of patients (mean age 67.4 years) discharged on low-dose aspirin from a Japanese academic hospital after coronary angiography. After three years follow-up, Miyake documented lower GI bleeding in 9 of 107 (8.4%), 5 of 173 (2.9%), and 4 of 258 (1.6%) patients discharged on PPI, H2RA, and neither PPI nor H2RA, respectively (Table 2 of this review). Controlled for hyperuricemia and warfarin use, Cox regression measured lower GI bleeding risk from PPI use vs. PPI or H2RA nonuse at HR 6.55, 95% CI 2.01-12.32 and from H2RA at HR 1.96, 95% CI 0.52-7.31.

4.1 Validity

DEPI found in Miyake serious risk of bias, with major concerns in two domains, confounding control and outcome measurement (ATTACHMENT 1). Either source for concern could explain an artificial association in Miyake between PPI and lower GI bleeding in patients on low-dose aspirin.

With respect to confounding control, seven disease covariates (older age, peptic ulcer disease, renal dysfunction, low ejection fraction, triple vessel disease, hypertension, and hyperuricemia) were more frequent at cohort entry in PPI users than in PPI or H2RA nonusers (Table 1). Use of three concomitant medications (calcium channel blockers, angiotensin receptor blockers, and α -glucosidase inhibitors) was more frequent at cohort entry in PPI users than in PPI or H2RA nonusers (Table 1). These differences align with practice guidelines, which (1) recognize older age and chronic illness as risk factors for GI complications from non-steroidal anti-inflammatory drugs (including low-dose aspirin) and (2) recommend PPI in patients with GI complication or cardiovascular disease risks (Lanza, et al., 2009). Miyake used Cox regression to adjust risk estimates for only two covariates (hyperuricemia and warfarin use) with nominal statistical associations with lower GI bleeding risk. As a practical matter, small study size, with only nine PPI-exposed cases of lower GI bleeding (Table 2), precluded satisfactory statistical control for differences between PPI users and PPI or H2RA nonusers.

With respect to outcome measurement, the case definitions used by Miyake required information from upper or lower GI endoscopy. However, the availability of this information depended on previous decisions by clinicians aware of patient histories. Consider the example of a 70 year-old man with mild asymptomatic anemia. In this setting, concurrent PPI specifically could bias

clinical decisions in favor of lower GI endoscopy, instead of upper GI endoscopy, leading to discovery of a possibly incidental abnormality (e.g., large colorectal adenoma), which fits the Miyake case definition for lower GI bleeding.

The strong PPI-associated 6-fold lower GI bleeding risk deserves notice. Confounding alone cannot entirely explain this strong association estimated by Miyake. Moreover, the differences between PPI-exposed and control patients, as shown in Table 1, should increase the baseline risks, in the PPI group, for both upper and lower GI bleeding. Yet, Miyake observed an upper GI bleeding risk lower in PPI patients than controls. Conversely, a bias specifically leading to detection in the PPI group of only a few lower GI bleeds could explain a substantial portion of the association observed by Miyake.

Finally, valid interpretation of the risk estimates reported by Miyake requires understanding of two points. First, Miyake studied outcomes in patients discharged on PPI, H2RA, or neither PPI nor H2RA. Miyake stopped follow-up when patients discontinued low-dose aspirin. However, the Miyake analysis did not account for PPI or H2RA users who discontinued use after discharge or PPI and H2RA nonusers who initiated use after discharge. Therefore, DEPI understands results from Miyake as estimates of excess risk observed in low-dose-aspirin patients on PPI at a fixed point in time, regardless of adherence subsequently. Second, Miyake ignored previous drug use when selecting and classifying patients at hospital discharge. Therefore, DEPI understands results from Miyake as estimates of excess risk observed in a mix of low-dose-aspirin patients, including both new and prevalent users of PPI.

4.2 Causality

DEPI found only weak evidence to support PPI as the causal explanation for the excess lower GI bleeding risk observed by Miyake in patients on low-dose aspirin (ATTACHMENT 2). As partial validation of method, Miyake reproduced a known causal association, protection against aspirin-associated upper GI bleeding by PPI or H2RA. In addition, through indirect comparison with nonuse, Miyake observed lower GI bleeding risks, higher after PPI than H2RA. However, statistical imprecision (wide confidence intervals) severely weakened the causal significance of this observation, which suggested an excess lower GI bleeding risk specific to PPI, as opposed to H2RA. Finally, a second Japanese case-control study (Nagata, et al., 2015) did not find excess lower GI bleeding risk from intermittent or regular use vs. nonuse in past month of PPI in patients on low-dose aspirin (adjusted odds ratio 1.02, 95% CI 0.62-1.68).

4.3 Public Health Implications

Any blood loss in older patients carries clinical significance. However, with respect to possible actions, (b) (4) FDA should note that the case definitions used by Miyake did not distinguish outcomes as either serious or non-serious adverse events, as defined by FDA. FDA actions should weigh the currently theoretical risks of lower GI bleeding against the accepted benefits of PPI against upper GI bleeding.

5. CONCLUSION

Serious risks of bias and weak evidence for causality severely limit the usefulness of results in

Miyake for FDA decision-making purposes.

6. RECOMMENDATIONS FOR DGIEP

DEPI recommends that DGIEP not use evidence from Miyake

(b) (4)

7. REFERENCES

Elwood, M, 1988, *Critical Appraisal of Epidemiology Studies and Clinical Trials*, 2nd edition, New York, Oxford University Press.

Lanza, FL, FK Chan, EM Quigley and G Practice Parameters Committee of the American College of, 2009, Guidelines for Prevention of NSAID-Related Ulcer Complications, *Am J Gastroenterol*, 104:728-38.

Miyake, K, T Akimoto, Y Hanada, H Nagoya, Y Kodaka, N Ueki, M Kusunoki, T Kawagoe, S Futagami, Y Takahashi, H Takano and C Sakamoto, 2015, Proton Pump Inhibitors Are Associated with Lower Gastrointestinal Tract Bleeding in Low-Dose Aspirin Users with Ischaemic Heart Disease, *Dig Liver Dis*, 47:757-62.

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

Sterne JAC, JPT Higgins, BC Reeves on behalf of the development group for ACROBAT-NRSI, September 2014, A Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24, Retrieved from <http://www.riskofbias.info> on June 29, 2015.

CC: C Wang / S Pinheiro / S Sandhu / E Wu / K Swank / A Winiarski / P Calloway (OSE)
D Griebel / J Korvick / A Rajpal / V Moyer / B Strongin / M Phan (DGIEP)

ATTACHMENT 1: Risk-of-bias assessment [1].

Domain	Risk of Bias Judgment	Support for Judgment
Bias due to confounding	Serious	Inadequate controls for age, sex, and other important comorbidities
Bias in selection of participants into the study	Moderate	Study participation required continuing care through a private academic hospital
Bias in measurement of interventions	Low	Documentation of PPI or H2RA, in medical records, at hospital discharge, accepted by DEPI as unrelated to study outcome
Bias due to departures from intended intervention	No information	No information provided on concomitant anticoagulants after cohort entry
Bias due to missing data	No information	82-85% follow-up through three years, but no information available about reasons for losses to follow-up
Bias in measurement of outcomes	Serious	Determinations of study outcome depended on medical decisions to perform upper or lower endoscopy for evaluation or treatment of anemia or GI bleeding; Primary examiners not blinded to clinical history at time of endoscopy
Bias in selection of the reported result	Moderate	Unknown if Miyake pre-specified the study purpose or analysis plan
Overall bias	Serious	Serious risk of bias in confounding and outcome domains

1. Sterne JAC, JPT Higgins, BC Reeves on behalf of the development group for ACROBAT-NRSI, September 2014, A Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24, Retrieved from <http://www.riskofbias.info> on June 29, 2015.

ATTACHMENT 2: Assessment for causation [1].

A. Description of evidence

1. Exposure Hospital discharge on PPI or H2RA as concomitant to low-dose aspirin
2. Outcome Clinical evidence for bleeding, defined by hematemesis, melena, bloody stool, hemoglobin drop ≥ 1.5 g/dL, or anemia (hemoglobin < 14 g/dL in men and < 12 g/dL in women), plus endoscopic evidence for bleeding source, (1) ≥ 3 mm ulcer with mucosal break, (2) vascular lesion with blood clot or active bleeding, or (3) tumor > 1 cm in diameter
3. Design Three-year follow-up in cohorts retrospectively constructed from medical records
4. Study population Coronary angiography patients, discharged between October 2005 and December 2006, from Nippon Medical School Hospital in Tokyo, Japan
5. Main result Lower GI bleeding risk, use of PPI vs. nonuse of PPI or H2RA, HR 6.55, 95% CI 2.01-12.32, p-value=0.002, controlled for hyperuricemia and warfarin use at cohort entry

B. Non-causal explanations

6. Observation bias See ATTACHMENT 1
7. Confounding See ATTACHMENT 1
8. Chance Primary study result based on only nine PPI users with lower GI bleeding (Table 2), with wide 95% CI, as noted under item #5, above

C. Features consistent with causation

9. Time relationship Exposure measured at hospital discharge, with bleeding outcomes occurring after hospital discharge; study design measured risks associated with initiating PPI or H2RA (intention-to-treat clinical trial analogue), but not risks associated with initiating and adhering to PPI or H2RA (per-protocol clinical trial analogue)
10. Strength Point estimate, 6-fold excess risk, considered strong
11. Dose response Not assessed
12. Consistency PPI associated with reduced upper GI bleeding risk
13. Specificity Lower GI bleeding risk stronger for PPI than H2RA

D. External validity

14. Eligible population Patients, from the source population, (1) not treated with coronary artery bypass grafting and (2) followed by physicians at the Nippon Medical School Hospital
15. Source population Patients discharged on low-dose aspirin, from a private academic hospital (Nippon Medical School Hospital), in Japan, after coronary angiography,
16. Target population Adults treated with low-dose aspirin for primary or secondary prevention of coronary heart disease

E. Consistency with other evidence

17. Consistency A second Japanese case-control study [2] measured lower GI bleeding risk from current PPI at adjusted odds ratio 1.02, 95% CI 0.62-1.68
18. Specificity Totality of evidence too limited for judgment
19. Plausibility PPI-associated change in intestinal microbiome offered as possible explanation for lower GI injury, with subsequent bleeding, in patients made susceptible by aspirin
20. Coherence Temporal correlation asserted between PPI popularity and declining ratio between upper

and lower GI complications

1. Elwood, M, 1988, *Critical Appraisal of Epidemiology Studies and Clinical Trials*, 2nd edition, New York, Oxford University Press.
2. Nagata, N, R Niikura, T Aoki, T Sakurai, S Moriyasu, T Shimbo, K Sekine, H Okubo, K Watanabe, C Yokoi, M Yanase, J Akiyama and N Uemura, 2015, Effect of Proton-Pump Inhibitors on the Risk of Lower Gastrointestinal Bleeding Associated with NSAIDs, Aspirin, Clopidogrel, and Warfarin, *J Gastroenterol*, 50:1079-86.

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/s/

JOEL L WEISSFELD
07/11/2016

SIMONE P PINHEIRO
07/11/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: November 19, 2014

To: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Errors Products
(DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): YOSPRALA (aspirin and omeprazole)

Dosage Form and Route: delayed-release tablets, for oral use

Application Type/Number: NDA 205-103

Applicant: Pozen Inc.

1 INTRODUCTION

On June 30, 2014, Pozen Inc. re-submitted for the Agency's review an original New Drug Application (NDA) 205-103 for YOSPRALA (aspirin and omeprazole) delayed-release tablets. The Division of Gastroenterology and Inborn Errors Products (DGIEP) considers the Applicant's re-submission to be a Class 2 complete response to the Agency's action letter issued on April 25, 2014. The proposed indication for YOSPRALA (aspirin and omeprazole) delayed-release tablets is for use in patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.

On July 11, 2014, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for YOSPRALA (aspirin and omeprazole) delayed-release tablets.

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for YOSPRALA (aspirin and omeprazole) delayed-release tablets.

2 CONCLUSIONS

Due to outstanding manufacturing deficiencies, DGIEP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

KAREN M DOWDY
11/19/2014

BARBARA A FULLER
11/19/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 8, 2014

Requesting Office or Division: Division of Gastroenterology and Inborn Error Products (DGIEP)

Application Type and Number: NDA 205103

Product Name and Strength: Yosprala (Aspirin and Omeprazole)
Delayed-release Tablets
325 mg/40 mg and 81 mg/40 mg

Submission Date: June 30, 2014

Applicant/Sponsor Name: Pozen Inc.

OSE RCM #: 2014-1930

DMEPA Primary Reviewer: Sherly Abraham, R.Ph.

DMEPA Team Leader: Kendra Worthy, Pharm.D.

DMEPA Associate Director: Lubna Merchant, M.S., Pharm.D.

1 PURPOSE OF MEMO

Pozen submitted their original NDA on March 25, 2013. On March 29, 2013, Division of Medication Error Prevention and Analysis (DMEPA)'s comments on carton and container labels were communicated to the sponsor. However, the application received a Complete Response on April 25, 2014. Pozen resubmitted the application to the Division on June 30, 2014 and revised label and labeling on July 28, 2014. Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the carton and container labels (Appendix A) to

determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container label and carton labeling are acceptable from a medication error perspective.

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

¹ Khosla, L. Label and Labeling Review for Yosprala (NDA 205103). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 12 3. 32 p. OSE RCM No.: 2013-993.

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/s/

SHERLY ABRAHAM
10/08/2014

KENDRA C WORTHY
10/08/2014

LUBNA A MERCHANT
10/08/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	YOSPRALA (ASPIRIN AND OMEPRAZOLE) DELAYED-RELEASE TABLETS, FOR ORAL USE
Applicant	Pozen, Inc.
Application/Supplement Number	NDA 205103
Type of Application	Original Submission
Indication(s)	YOSPRALA tablets are 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. The aspirin component of YOSPRALA is indicated for (1) 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, (2) reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, (3) reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, (4) use in patients who have undergone revascularization procedures (CABG, PTCA) when there is a pre-existing condition for which aspirin is already indicated. The omeprazole component of YOSPRALA is indicated for decreasing the risk of developing aspirin associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (\geq 55) or documented history of gastric ulcers.
Office/Division	ODE III/DGIEP
Division Project Manager	Stacy Barley
Date FDA Received Application	March 25, 2013
Goal Date	April 25, 2014
Date PI Received by SEALD	April 23, 2014
SEALD Review Date	April 24, 2014
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *HL is greater than 1/2 page. Waiver granted by DGIEP.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Selected Requirements of Prescribing Information

Comment: HL Indications and Usage, first paragraph should reference "(1.1)", not "(1)." HL Dosage and Administration, the reference at the end of the first sentence is missing. Insert "(2)". HL Warnings and Precautions, 6th bulleted item does not reference to W&P section. Insert correct W&P reference instead of "(1.2)."

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: Insert name of drug product (i.e., YOSPRALA), (b) (4) "

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Selected Requirements of Prescribing Information

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

NO 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *There is no established pharmacologic class listed in HL. DGIEP to follow-up.*

Dosage Forms and Strengths in Highlights

N/A

Selected Requirements of Prescribing Information

20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: The bolded statement must read: See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. It currently reads [REDACTED] ^{(b) (4)}

[REDACTED] Please correct.

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment: [REDACTED] (b) (4)
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: [REDACTED] (b) (4)
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

(b) (4)

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: For subsections 5.4 and 5.5, must use the section heading in the cross reference as designated by regulation (i.e. Use in Specific Populations (b)(4)):

(b)(4) The same comment applies to subsection 12.2, 2 paragraph, cross reference to section, not subsection heading - [see Clinical Pharmacology (12.3)], (b)(4)]. Also, subsection 8.4, 1st paragraph cross reference must read [see Contraindications (4)], (b)(4)]. (b)(4)
Clinical Studies section, 1 paragraph, cross reference should read: (b)(4)

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment: The FPI heading should be left justified, not centered in the middle of the page.

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- NO** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *All FDA-approved patient labeling must appear at the end of the PI upon approval. The Medication Guide does not appear at the end of the PI.*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JEANNE M DELASKO
04/24/2014

ERIC R BRODSKY
04/24/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 22, 2014

To: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): YOSPRALA (aspirin and omeprazole)

Dosage Form and Route: delayed release tablets

Application Type/Number: NDA 205-103

Applicant: Pozen Inc.

1 INTRODUCTION

On March 25, 2013, Pozen Inc. submitted for the Agency's review an original New Drug Application (NDA) 205-103 for YOSPRALA (aspirin and omeprazole) delayed release tablets, with the proposed indication for use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers. On December 18, 2013, the Applicant submitted a response to a Clinical Information Request. The Agency considers the December 18, 2013 submission to be a major amendment to the original NDA application.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on April 24, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for YOSPRALA (aspirin and omeprazole) delayed release tablets.

2 MATERIAL REVIEWED

- Draft YOSPRALA (aspirin and omeprazole) delayed release tablets Medication Guide (MG) received on April 30, 2013, and received by DMPP and OPDP on April 15, 2014.
- Draft YOSPRALA (aspirin and omeprazole) delayed release tablets Prescribing Information (PI) received on March 25, 2013 and further revised on April 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 15, 2014.
- Approved PRILOSEC (omeprazole) delayed-release capsules comparator labeling dated March 27, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
04/22/2014

MEETA N PATEL
04/22/2014

SHARON R MILLS
04/22/2014

LASHAWN M GRIFFITHS
04/22/2014

NDA 2015103 PMC Development: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC /PMC types

NDA/BLA #
Product Name:

NDA 205-103 Yosprala

(b) (4)

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/s/

BANU S ZOLNIK
04/22/2014

SANDRA SUAREZ
04/22/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: April 21, 2014

To: Stacy Barley, RN, MSN, MSHA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205103
OPDP Comments for draft Yosprala (aspirin and omeprazole) delayed
release tablets

OPDP has reviewed the proposed draft Yosprala (aspirin and omeprazole) delayed release tablets Prescribing Information (PI). We have reviewed the draft PI, sent to us on April 14, 2014, and have the following comments. The Medication Guide will be reviewed jointly with DMPP and sent under a separate cover.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
04/21/2014



Center for Drug Evaluation and Research

Division of Cardiovascular and Renal Products

Consultation, NDA 205103

DATE: Consult requested: 30 April 2013
Consult request amended: June 07, 2013
Consult request amended: 18 September 2013
Desired completion date: 23 September 2013
Consult amended: 18 Oct 2013
Consult completed: 18 September 2013

FROM: Preston M. Dunnmon, M.D., Medical Officer
Division of Cardiovascular and Renal Products, HFD-110

Sudharshan Hariharan, Ph.D., Reviewer
Office of Clinical Pharmacology, DCP1

Rajanikanth Madabushi, Ph.D., Team Leader
Office of Clinical Pharmacology, DCP1

THROUGH: Norman Stockbridge, M.D., Ph.D., Division Director
Division of Cardiovascular and Renal Products, HFD-110

Stephen M. Grant, M.D., Deputy Director
Division of Cardiovascular and Renal Products, HFD-110

TO: CDR Anissa Davis, SRPM, DGIEP, 301-796-5016
CDR Stacy Barley, SRPM, DGIEP, 301-796-2137

SPONSOR: POZEN, Inc.
DRUG CLASS: Combination Proton Pump Inhibitor and Aspirin
DRUG NAME: PA8140 and PA32540 (enteric coated aspirin/immediate release omeprazole)

FORMULATION: PO
APPLICATION No: NDA 205103

PROPOSED INDICATION:

(b) (4)

DOCUMENTS AVAILABLE FOR REVIEW: NDA 205103

1. BACKGROUND

PA Tablets were developed as a PPI and aspirin containing tablet in a coordinated delivery system that is intended to provide the cardio-protective benefits of aspirin while reducing aspirin-related UGI damage and thus improving adherence.

This 505(b)2 application presents pharmacokinetic and pharmacodynamic data on PA Tablets to establish the bridge to the reference listed drugs (RLD) Ecotrin[®] (325 mg and 81 mg) and Prilosec[®].

Clinical safety and efficacy were assessed in 1429 subjects with a history of established cardiovascular disease receiving daily 325 mg aspirin and at risk of developing aspirin-associated gastric ulcers in the two controlled studies of 6-months duration (PA32540-301 and PA32540-302) as well as in a 12-month, open-label, safety study (PA32540-303).

Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Cardiovascular and Renal Products (DCaRP) about questions related to (i) review of major adverse cardiovascular events in patients receiving clopidogrel concomitantly from the efficacy trials, (ii) lack of bioequivalence of the aspirin components between PA32540 and Ecotrin[®] 325 mg, (iii) review of PLR labeling specific to the aspirin component, and (iv) drug interaction potential of the omeprazole component in PA32540 with clopidogrel. These consult questions are listed below in detail along with appropriate responses.

2. CONSULT QUESTIONS

Q.1 Applicant has provided an Integrated Summary of Safety of data from Studies 301 and 302 that includes an analysis of Cardiovascular Events of Special Interest (Section 2.4.2). MACE were observed in both studies and applicant also provides an analysis of MACE in patients who received clopidogrel concomitantly. Do the adjudicated and unadjudicated analyses presented by the sponsor, including the analysis of MACE in subjects who took clopidogrel, warrant inclusion in the label? Do these analyses suggest a new safety concern?

Critical to any assessment of cardiac safety is an understanding of the trial designs, populations assessed, pooling methods, population exposures, ascertainment methodologies for MACE events, data flow to the clinical events committee (CEC), MACE definitions, and MedDRA preferred term groupings (i.e., SMQs) that were used as automated system triggers for identifying potentially missed MACE outcome events

based on manual reporting. Understanding these elements, the actual MACE data can be reasonably interpreted. For this sponsor's development program, a summary of these important components are as follows.

Phase 3 Trials

PA32540-301: A 6-Month, Phase 3, Randomized, Double-Blind, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric-Coated Aspirin 325 mg in Subjects Who Are at Risk for Developing Aspirin-Associated Ulcers

- Males or non-pregnant, non-breastfeeding females who had been on daily (at least 5 days per week) aspirin 325 mg for at least 3 months and who were expected to use daily aspirin 325 mg for at least 6 months, and who were
 - 55 years of age and older; or
 - 18-54 years of age with a history of a documented gastric or duodenal ulcer within the past 5 years
- Aspirin was used for the secondary prevention of the following cardiovascular or cerebrovascular events:
 - Diagnosis or history of:
 - Confirmed or suspected myocardial infarction (MI);
 - Ischemic stroke; or
 - Transient ischemic attack (TIA).
 - Or established, clinically significant coronary and other atherosclerotic vascular disease (i.e., high risk for surgical intervention or for MI, TIA, stroke, if left untreated), including:
 - Angina (stable or unstable);
 - Peripheral arterial disease;
 - Atherosclerotic aortic disease; or
 - Carotid artery disease.
 - Or history of:
 - Coronary artery bypass graft (CABG);
 - Percutaneous coronary intervention (PCI) with or without stent; or
 - Carotid endarterectomy.

PA32540-302: A 6-Month, Phase 3, Randomized, Double-Blind, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric-Coated Aspirin 325 mg in Subjects Who Are at Risk for Developing Aspirin-Associated Ulcers

- Same eligibility criteria as study 301

PA32540-303: A 12-Month, Phase 3, Open-Label, Multi-Center Study to Evaluate the Long-Term Safety of PA32540 in Subjects Who Are at Risk for Developing Aspirin-Associated Gastric Ulcers

- Same eligibility criteria as studies 301 and 302

Population Definitions

Primary Safety Population (PSP) - all subjects randomized in the 6-month active-controlled studies PA32540-301 and PA32540-302. The adverse events seen in subjects who were treated with PA32540 are directly compared to those subjects who were treated with EC-aspirin 325 mg.

Long-term Safety Population (LSP) - all subjects who entered open-label study PA32540-303 and received at least one dose of PA32540 drug in study PA32540-303.

Twelve-Month Population (TMP) - subjects from open-label study PA32540-303 that completed at least 348 days of treatment with PA32540

Six-Month Population (SMP) - subjects from studies PA32540-301, PA32540-302 and PA32540-303 who were on treatment at least 168 days

Normal Healthy Volunteers (NHV) - subjects from the NHV studies were not pooled for safety analysis with patients from studies 301, 302, and 303 due to the variable designs of these studies (including cross-over designs).

Extent of exposure

Overall, 1221 subjects were exposed to PA32540 for up to 12 months. Of these, 321 subjects were healthy volunteers in eleven Phase 1 studies and 900 subjects were exposed in the three Phase 3 studies. Of the 900 Phase 3 subjects, 735 were exposed for 6 months and 290 for 12 months (Clinical Summary of Safety Section 2.7.4.1.2), a total of 548 patient years of exposure (ISS Table S1.3.1). Eighty-six subjects were exposed to PA8140. (Clinical overview page 22)

Table 2: Exposure by Population, PA Tablets and EC-aspirin

	Subjects	
	PA32540	EC-aspirin 325 mg
All Studies	1221	803
NHV	321	279
All Phase 3	900	524
Population		
Primary Safety Population (PSP)	521	524
Long-term Safety Population (LSP)	379	NA
Twelve Month Population (TMP)	290	NA
Six Month Population (SMP)	735	366
	Subjects	
	PA8140	EC-aspirin 81 mg
NHV	86	126

Note: NA = not applicable.

Source: Table S1.1, Table S1.2, Table S.1.3, Table S2.1, and Table S3.1; Table 14.1.1, PA08140-101; Table 14.3.1, PA8140-102; Table 14.1.1, PA325-102; Table 14.1.1, PA32540-111; Table 14.1.1, PA32540-303.

MACE Ascertainment and Definitions

An independent Cardiovascular Review Committee (CRC), consisting of 3 Board Certified cardiologists who had staff level experience or privileges as a cardiologist at a medical institution performed a blinded review and adjudication of major adverse cardiovascular events (MACE). Briefly, the POZEN Medical Monitor (MM) reviewed all cardiovascular events identified by the sites and study monitors for CRC review. If the POZEN MM agreed the event may constitute a potential MACE, the event was reviewed by the CRC. If the POZEN MM did not agree, the CRC Chair reviewed the AE and if he determined the event constituted a potential MACE, the event was reviewed by the CRC. In addition, the POZEN MM periodically reviewed the clinical database and AE Listings and the CRC Chair reviewed the cardiovascular AEs and all SAEs for potential clinically significant cardiovascular events that might have not been identified by the sites. The CRC adjudicated events to a MACE category using the criteria listed below (from ISS Table 5, pg 44):

Table 5: Cardiovascular Events and Definitions

Cardiovascular Event	Definition¹
Cardiovascular Death	
Sudden cardiac death (SCD):	An unexpected death in a previously stable patient. Patients in this category should have had recent human contact before the event. This includes patients who after attempted resuscitation were comatose and then died. Patients who have been out of contact for a prolonged or unknown period of time should be classified as unknown.
Fatal myocardial infarction (MI):	Death from a cardiac event within 28 days of acute MI (including sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST elevation or new left bundle branch block (LBBB), and/or evidence of fresh thrombus by a coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood).
Pump failure death:	Death involving a substantive worsening of heart failure symptoms and/or signs resulting in augmentation or addition of heart failure therapies (O'Connor 2010).
Death due to stroke:	Death involving cerebral hemorrhage, cerebral infarct or cerebral embolism, in the absence of an MI.
Cardiac Procedure Death:	Death within 30 days of and related to a cardiac procedure.
Other Cardiovascular:	Death in which there is evidence of a primary cardiovascular etiology that cannot be classified as definite sudden death, MI, pump failure, stroke, or procedure-related (e.g., ruptured aortic aneurysm, aortic dissection, pulmonary embolism, cardiac tamponade).
Non-Fatal Events	
Non-Fatal MI	<p>Non-fatal MI was defined as presentation in a clinical setting consistent with myocardial ischemia with evidence of myocardial necrosis and alive 7 days after the index event. Non-fatal MI will also be characterized by Type as per UDMI criteria.</p> <p>Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:</p> <ul style="list-style-type: none">• Symptoms of ischemia• Electrocardiogram (ECG) changes indicative of new ischemia (new ST-T changes or new LBBB)• Development of pathological Q waves in the ECG• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Cardiovascular Event	Definition¹
Non-Fatal MI	<p>For percutaneous coronary interventions (PCI) in subjects with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.</p> <p>Stent thrombosis will be adjudicated according to Academic Research Consortium (ARC) criteria. Events judged as “definite” and “probable” stent thrombosis will meet this definition.</p> <p>For coronary artery bypass grafting (CABG) in subjects with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically-documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.</p> <p>Subjects presenting after randomization for routine evaluation or other reasons and who are found to have evidence of interval prior MI will be defined to have had non-fatal MI. Any one of the following criteria meets the diagnosis for prior MI:</p> <ul style="list-style-type: none"> • Development of new pathological Q waves with or without symptoms. • Imaging evidence of a region of loss of viable myocardium that is thinned • and fails to contract, in the absence of non-ischemic cause. • Pathological findings of a healed or healing MI.
Confirmed Ischemic Stroke	<p>Stroke is defined as a rapidly developing loss of brain function that is non-reversible and due to an interruption in the blood supply to all or part of the brain, and that persists for more than 24 hours, together with a diagnostic imaging study. PA32540 Phase 3 Program Page 9 of 10, Cardiovascular Review Committee Charter Version 1.0</p>
Unplanned Coronary Artery Bypass Graft Surgery	<p>Any Coronary Artery Bypass Graft Surgery that was unplanned prior to entry into the study</p>
Unplanned Percutaneous Coronary Intervention	<ul style="list-style-type: none"> • Any unplanned PCI, including any mechanical catheter-based revascularization techniques such as stenting, balloon angioplasty, coronary atherectomy or laser therapy. • Other surgical-based cardiac revascularization techniques (e.g., transmyocardial revascularization)

Cardiovascular Event	Definition ¹
Acute Coronary Syndromes (ACS)	Acute coronary syndromes are defined as a group of clinical syndromes compatible with acute myocardial ischemia, ranging from ST-segment elevation myocardial infarction (MI) to non-ST segment elevation MI and unstable angina. ACS without biological marker (unstable angina without detectable myocyte necrosis) is defined as non-ST-segment elevation ACS not accompanied by the release of markers of cell death (troponin and CK-MB), and is typically characterized by ECG changes of ST-segment depression or T-wave inversion or transient ST-elevation (Fox 2004a).
Other Adverse Cardiovascular Events	<ul style="list-style-type: none"> Heart failure or signs and symptoms of heart failure requiring hospital admission or emergency room visit and requiring intravenous therapy Transient ischemic attack less than 24 hours old, defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton 2009).
Non-Cardiovascular Deaths	<ul style="list-style-type: none"> Death due to causes such as infection, bleed, pulmonary, renal, cancer or other non-cardiovascular etiologies. Unknown death, defined as confirmed death, but without data to support mode of death. Death outside of the hospital without adequate source documentation or medical records will require a case narrative to be submitted by the investigator.

¹ Source: Appendix 9.5.1.1

MACE Data from Blinded Controlled Phase 3 Trials

The sponsor's analysis of treatment-emergent MACE (unadjudicated MACE) was based on a smaller set of preferred terms than used by the CEC for adjudicated MACE. Therefore, the listing of unadjudicated MACE events is smaller than was the case for adjudicated events. Importantly, the adjudicated MACE listing contained all of the unadjudicated MACE events. Summary results for both non-adjudicated and adjudicated MACE are shown below (from ISS table 59, pg 132, Primary Safety Population):

Table 59: Major Cardiovascular Events (MACE): Non-Adjudicated and Adjudicated Events

	Major Cardiovascular Events (MACE)					
	PA32540 N=521			EC-aspirin 325 mg N=524		
	Total Patient-Years =226.91			Total Patient-Years= 212.05		
	Event	Subject	Events Per 100 Patient Years Exposure	Event	Subject	Events Per 100 Patient Years Exposure
Non Adjudicated	6	5 (1.0%)	2.6	4	4 (0.8%)	1.9
Adjudicated	9	9 (1.7%)	4.0	14	13 (2.5%)	6.6

Source: S2.19.1, S1.3.1; and Table 14.3.2.2, PA32540-303; and ISS Appendix 9.5.1.4.

Noted is the fact that the adjudicated MACE rate for the PA32540 population was numerically lower when the CEC's more comprehensive dataset is used to count MACE events. The sponsor listed the breakdown of the MACE events, which for the non-adjudicated cases are as follows (from ISS table 54, pg 127, PSP, N=521 for PA32540, N= 524 for EC-aspirin 325mg):

Table 54: Subjects with Treatment Emergent Pre-Specified Major Cardiovascular Events (MACE) in the Primary Safety Population (PSP)

Study - Site / Subject	MACE	Adverse Event Preferred Term
PA32540		
302-499/3015	Non-Fatal Myocardial Infarction CV Death	Acute Myocardial Infarction Cerebrovascular Accident
302-572/4238	Non-Fatal Myocardial Infarction	Myocardial Infarction
302-676/4225	Non-Fatal Myocardial Infarction	Myocardial Infarction
302-860/4612	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction
302-862/4637	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction
EC-aspirin 325 mg		
301-455/2241	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction
301-509/1033	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction
302-664/4388	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction

Source: Table S2.19.1 excluding one non-treatment emergent adverse event (subject 301-887/2639).

All of these cases captured by the sponsor were also identified by the CEC using the broader preferred term screen, as is see below (from ISS table 55, pg 128, PSP, N=521 for PA32540, N= 524 for EC-aspirin 325 mg):

Table 55: Adjudicated Major Cardiovascular Adverse Events (Expanded Terms) in Primary Safety Population (PSP)

Study - Site / Subject	MACE Category	Adverse Event Preferred Term
PA32540		
301-856/2645	CAD	Non-Cardiac Chest Pain
302-676/4225	Non fatal MI	Myocardial Infarction
302-572/4238	Non fatal MI	Myocardial Infarction
302-860/4612	Non fatal MI	Acute Myocardial Infarction
302-862/4637	Non fatal MI	Acute Myocardial Infarction
302-499/3015	Non fatal MI	Acute Myocardial Infarction
302-860/4515	Planned Coronary Artery Bypass Graft	Arteriosclerosis Coronary Artery
302-489/4466	TIA	Reversible Ischaemic Neurological Deficit
302-660/3027	Heart Failure	Cardiac Failure Congestive
EC-aspirin 325 mg		
301-455/2241	Non fatal MI	Acute Myocardial Infarction
301-509/1033	Non fatal MI	Acute Myocardial Infarction
302-664/4388	Non fatal MI	Acute Myocardial Infarction
301-776/2650	ACS	Coronary Artery Occlusion
301-776/2650	ACS	Angina Pectoris
302-379/4241	ACS	Angina Pectoris
301-647/2532	TIA	Transient Ischaemic Attack
301-792/2505	TIA	Transient Ischaemic Attack
301-887/2639	CV Death	Sudden Cardiac Death
302-655/4256	ACS	Coronary Artery Disease
302-700/4421	ACS	Angina Pectoris
302-787/4604	TIA	Transient Ischaemic Attack
302-379/4302	TIA	Reversible Ischaemic Neurological Deficit
302-849/4653	Heart Failure	Cardiac Failure Congestive

Source: Table S2.19.1; and Appendix 9.5.1.4.

Reviewer's comment: As expected AMI and ACS predominate, with few cerebral vascular and CHF events.

Of note, the most striking differential outcome between the PA32540 and EC-aspirin 325 groups were based on the use of clopidogrel co-therapy, as seen below (from ISS table 56, pg 129, PSP, N=521 for PA32540, N= 524 for EC-aspirin 325 mg):

Table 56: Proportion of Subjects with Pre-Specified Major Cardiovascular Adverse Events by Concomitant Use of Clopidogrel in the Primary Safety Population from Studies PA32540-301 and PA32540-302

	Clopidogrel Use = Yes ¹				Clopidogrel Use = No	
	PA32540 n(%) (N=117)		EC-Aspirin 325 mg n(%) (N=115)		PA32540 n(%) (N=404)	EC-Aspirin 325 mg n(%) (N=409)
	Any Time	Within 7 Days	Any Time	Within 7 Days		
Subjects with Any Major CV AE	4 (3.4)	4 (3.4)	0	0	1 (0.2)	4 (1.0)
Non-Fatal Stroke	0	0	0	0	0	0
Non-Fatal Myocardial Infarction	4 (3.4)	4 (3.4)	0	0	1 (0.2)	3 (0.7)
CV Death	0	0	0	0	1 (0.2)	1 (0.2)

¹'Any Time' columns include subjects on clopidogrel at any time during the treatment period. 'Within 7 Days' columns include only MACE Adverse Events that occurred following at least 7 consecutive days of clopidogrel use.

Source: Table S2.19

DCRP Conclusions for Question 1:

- The number of events is too small and the duration of exposure too short to draw reliable conclusions about cardiac safety. Rather than including Table 59 above that demonstrates these small numbers (with more unadjudicated MACE events and fewer adjudicated MACE events with this drug), we suggest including a statement that simply states that the number of adjudicated MACE events was similar between the groups, but number of events is too small and the duration of exposure too short to draw reliable conclusions about cardiac safety.
- Even in this small dataset, all MACE events in clopidogrel-treated patients occurred in the group receiving omeprazole (as PA32540). Given the well-known interaction between clopidogrel and omeprazole, the label for PA32540, if approved, should reflect the warning regarding clopidogrel and omeprazole as is currently included in the omeprazole label.

Q.2 According to sponsor's analysis, PA32540 (test product) was not bioequivalent to Ecotrin 325 mg (reference product) in terms of bioavailability parameters of acetylsalicylic acid in a BE study using reference-scaled average bioequivalence approach. The point estimate for exposure (AUC) to acetylsalicylic acid was 10-15% lower for PA32540 Tablets compared to Ecotrin 325 mg, however, the lower limit of the 90% confidence interval was outside the scaled BE range. The sponsor states that: "These results suggest that some subjects may absorb slightly less than the intended 325mg of aspirin. Because the relevant antithrombotic effects of aspirin have been demonstrated to occur over the dose range of 50-325mg, this observed small difference in acetylsalicylic acid exposure is not clinically meaningful." Does DCRP agree with sponsor's statement?

The only generally accepted and well-understood mechanism by which aspirin reduces the risk of adverse CV events is through inhibition of platelet aggregation via irreversible

acetylation of the cyclooxygenase-1 (COX-1) enzyme. Inhibition of COX-1 prevents conversion of arachidonic acid to thromboxane A2 (TxA2), which a potent agonist of platelet aggregation and therefore of thrombosis. Dose-response studies with aspirin have been conducted in past. A publication from Patrignani *et al*¹ shows that aspirin produces greater than 90% inhibition of serum thromboxane B2 (TxB2, the stable breakdown product of TxA2) following a single 100- mg dose. Upon repeat dosing at 0.45 mg/kg (equivalent to 31.5 mg for a 70 kg human), the authors report 95% inhibition of serum TxB2 by day 4. Similar results were also reported by Buerke and colleagues² where >95% inhibition of serum TxB2 was achieved by day 7 with 40 mg of loading and maintenance dose of aspirin which was no different when compared to aspirin treatment regimens with initial loading doses of 100, 300 or 500 mg and maintenance doses of 40 or 100 mg. The results provide evidence that upon repeat administration near maximal inhibition of serum TxB2 is attained at aspirin doses 81 mg or lower. Therefore, 10-15% lower exposure to aspirin for PA32540 tablets compared to Ecotrin[®] 325 mg is not clinically meaningful as this change in aspirin plasma exposures at 325 mg does not affect platelet inhibition.

The discussion above begs the question whether anyone "needs" high dose maintenance aspirin, as was tested in this development program, for the secondary prophylaxis if CV events. The STEMI and NSTEMI guideline writing committees for the American College of Cardiology have recently re-evaluated the evidence for aspirin dosing in which the low dose of aspirin was given a Class IIa recommendation as opposed to higher doses of aspirin. Evidence to support this recommendation came first from the "Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death (CV or unknown cause), non-fatal myocardial infarction, and non-fatal stroke in high risk patients" (BMJ. 2002;324:71-86). This meta-analysis had the following important design elements and outcomes:

- Information about serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) was available from 195 trials of antiplatelet treatment versus control
- 7705 (10.7%) serious vascular events were recorded among 71,912 high risk patients allocated antiplatelet therapy versus an adjusted total of 9502 (13.2%) among 72,139 allocated control (P < 0.0001)
- The effects of different dose ranges of aspirin were assessed. At or above 75 mg per day, no particular range of aspirin dose was preferable for the prevention of serious vascular events. The proportional reduction in vascular events was:
 - 19% with 500-1500 mg daily
 - 26% with 160-325 mg daily
 - 32% with 75-150 mg daily,
 - 13% for daily doses <75 mg
- A figure of these results is shown below (slide from the ACCF 2013 Board Review, de Lemos):

¹ Patrignani P, Filabozzi P, Patrono C. *J Clin Invest.* 1982 Jun;69(6):1366-72.

² Buerke M, Pittroff W, Meyer J, Darius H. *Am Heart J.* 1995 Sep;130:465-72.

Indirect Comparisons of ASA Doses on Vascular Events in High-Risk Patients



* Odds reduction.

Treatment effect $P < .0001$.

ASA, acetylsalicylic acid.

Adapted with permission from BMJ Publishing Group, Antithrombotic Trialists' Collaboration.

BMJ. 2002;324:71-86.

Subsequently, the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) investigators evaluated the benefits and risks of adding clopidogrel to different doses of aspirin in the treatment of patients with acute coronary syndrome (ACS) (Circ. 2003; 108:1682-1687). The CURE trial and its aspirin-substudy assessing outcomes by aspirin dose had the following important design elements and outcomes:

- A double-blind, placebo-controlled trial of 12,562 patients with ACS receiving aspirin, 75 to 325 mg daily, randomized to clopidogrel or placebo for up to one year.
- The two primary outcomes of the CURE trial were
 - The composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke, and
 - The composite of the first primary outcome or refractory ischemia.
- The secondary outcomes were severe ischemia, heart failure, and the need for revascularization.
- Major bleeding was defined as being significantly disabling, intraocular bleeding leading to significant loss of vision, or bleeding requiring transfusion of 2 or 3 units of red blood cells or equivalent whole blood. Major bleeding was subclassified as life-threatening or other major bleeding. Life-threatening bleeding complications were defined as fatal or leading to a drop in hemoglobin of ≥ 5 g/dL or significant hypotension with the need for inotropes, requiring surgery (other than vascular site repair) or symptomatic intracranial hemorrhage, or requiring transfusion of 4 or more units of red blood cells or equivalent whole blood.

- In the CURE aspirin substudy analysis, patients were divided into the following 3 aspirin dose groups: ≤ 100 mg, 101 through 199 mg, and ≥ 200 mg.
- The combined incidence of cardiovascular death, myocardial infarction, or stroke was reduced by clopidogrel regardless of aspirin dose, as follows: ≤ 100 mg, 10.5% versus 8.6% (relative risk [RR], 0.81 [95% CI, 0.68 to 0.97]); 101 to 199 mg, 9.8% versus 9.5% (RR, 0.97 [95% CI 0.77 to 1.22]); and ≥ 200 mg, 13.6% versus 9.8% (RR, 0.71 [95% CI, 0.59 to 0.85]).
- GI bleeding increased significantly with increasing aspirin dose in both the placebo and the clopidogrel groups (from publication text – data not shown)
- The incidence of major bleeding increased with increasing aspirin dose both in the placebo group (1.9%, 2.8%, and 3.7%, respectively; $P=0.0001$) and the clopidogrel group (3.0%, 3.4%, and 4.9%, respectively; $P=0.0009$), as seen in the figure below:

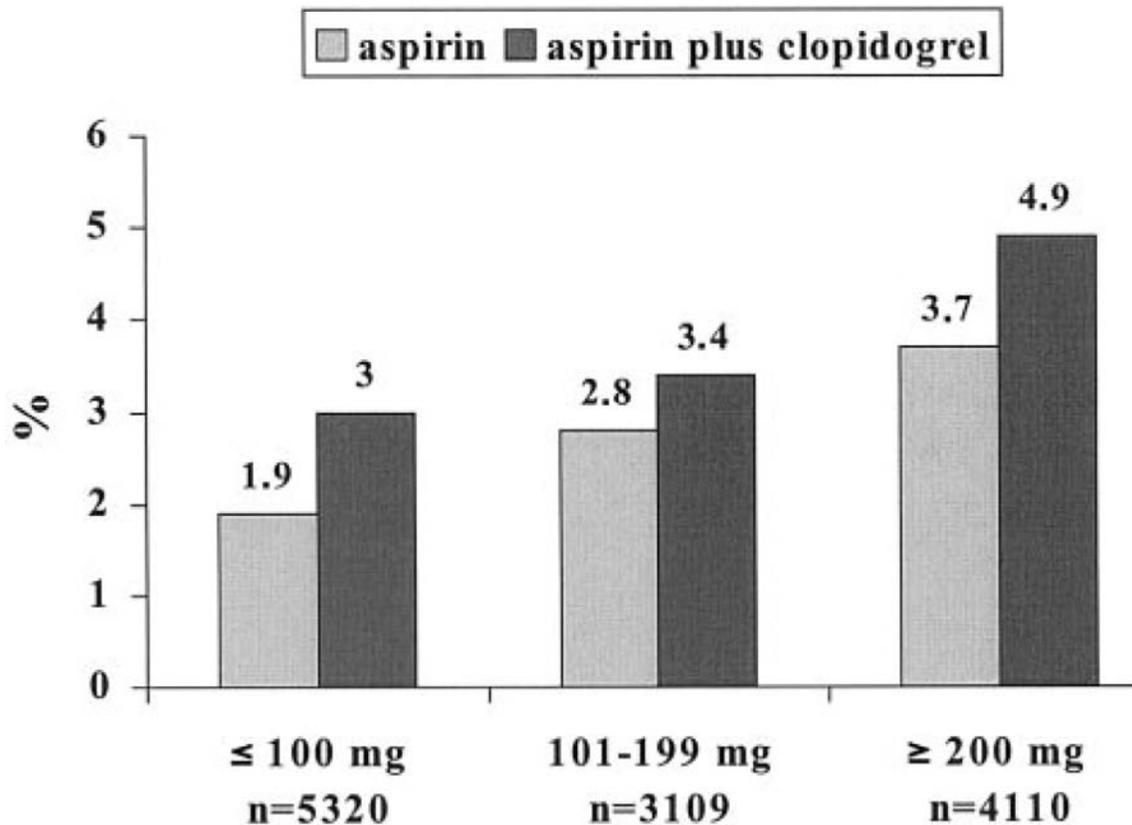


Figure 3. Aspirin dose and the incidence of major bleeding.

Further evidence suggesting an increase in major bleeding with increasing doses of aspirin without offsetting incremental efficacy in patients with CV disease and/or hypertension came from a large meta-analysis by Serebrauny et al (Am J Card 2005;95:1218). In this meta-analysis, major bleeding events were defined differently across the 31 studies (192,036 patients) that were eligible for analysis (mostly TIMI and

GUSTO definitions). The trials included in this meta-analysis are shown in the table below from that publication:

Trial (ref no.)	Total in the trial (n)	Patients on ASA (n)	Bleeding Events*					
			Total	Minor	GI	Major	Fatal/life Threat	Stroke
ASA <100 mg								
DUTCH TIA ⁸	3,131	1,555	89	49	14	40	11	13
ESPS-2 ⁹	6,602	1,649	135			20		
SAPAT ¹⁰	2,035	1,009	27	7	11	20		5
HOT ¹¹	1,879							
	0	9,399	292	156	102	129	7	14
Thrombosis prevention trial ¹²	5,499	1,268		484	5	8		2
SALT ¹³	1,360	676	49		9	20	10	
CURE ²	6,303	948	35	4	6	19	6	1
ACE ¹⁴	2,849	698			8	12	2	4
PPP ¹⁵	4,495	2,226	24		17			2
ASA 100–200 mg								
2nd SYMPHONY ¹⁶	6,671	2,231		234		89		1
SYMPHONY ¹⁷	9,172	3,074	570	386		120		1
STAMI ¹⁸	1,470	736				7		
	1,335							
PEP ¹⁹	9	6,679				13		
CARS ²⁰	8,803	3,281				57		
	2,110							
CAST ²¹	6	10,554				86	39	115
CHAMP ²²	5,059	2,357		77		50	7	15
CURE ²	6,303	3,311	152	43	13	77	29	1
ASA >200 mg								
DUTCH TIA ⁸	3,131	1,576	137	84	21	53	18	15
EAF ²³	1,007	404		29	10	6	6	2
AFASAK 2 ²⁴	677	169	31	26		5		1
MUST-I ²⁵	622	153						1
UK-TIA ²⁶	2,435	810			25			7
STARS ²⁷	1,965	557	10					
ACE ¹⁴	2,849	697			6	13	2	6
	1,943							
IST ²⁸	5	9,720						87
	8,767							
US NURSE ²⁹	8	87,678						62
	2,207							
PHSRG ³⁰	1	11,037				364		23
SPAF-II ³¹	1,100	545						6
	1,718							
ISIS-2 ³²	7	8,587						5
	1,918							
CAPRIE ³³	5	9,586	890		255	149		47
CREDO ³⁴	2,116	1,063		59		71		
WARSS ³⁵	2,206	1,103		259		30	5	
SPAF-III ³⁶	892	892				11		2
CURE ²	6,303	2,044	297	107	28	81	78	3
ACE ¹⁴	2,849	703			8	18	3	9
TASS ³⁷	3,069	1,540	152					
ACE ¹³	2,849	706			8	17	3	8
UK-TIA ²⁶	2,435	815			39			7

The meta-analysis demonstrated a dose-responsive relationship with aspirin and major bleeding that was statistically significant, as shown in the figure below from that publication:

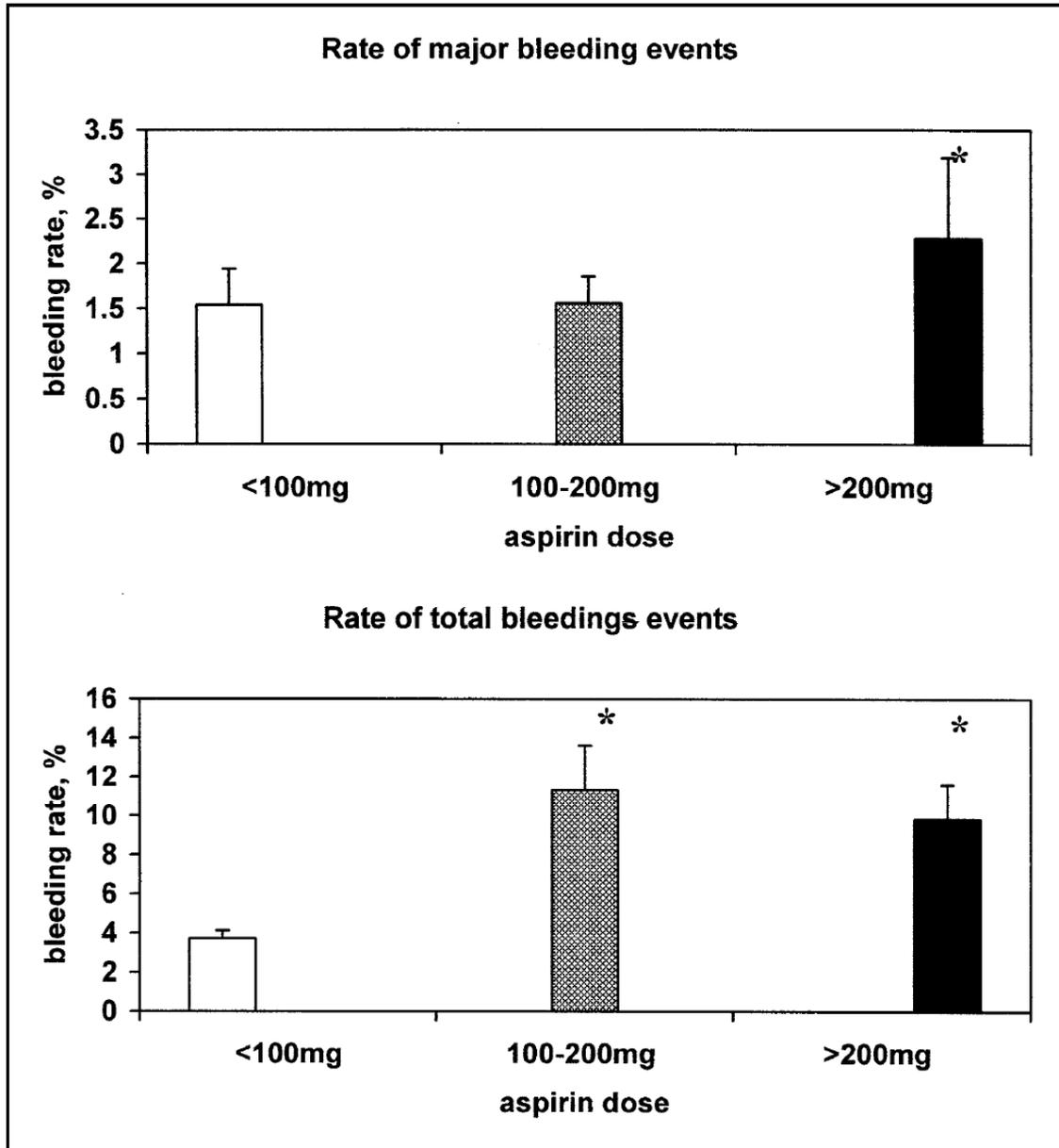
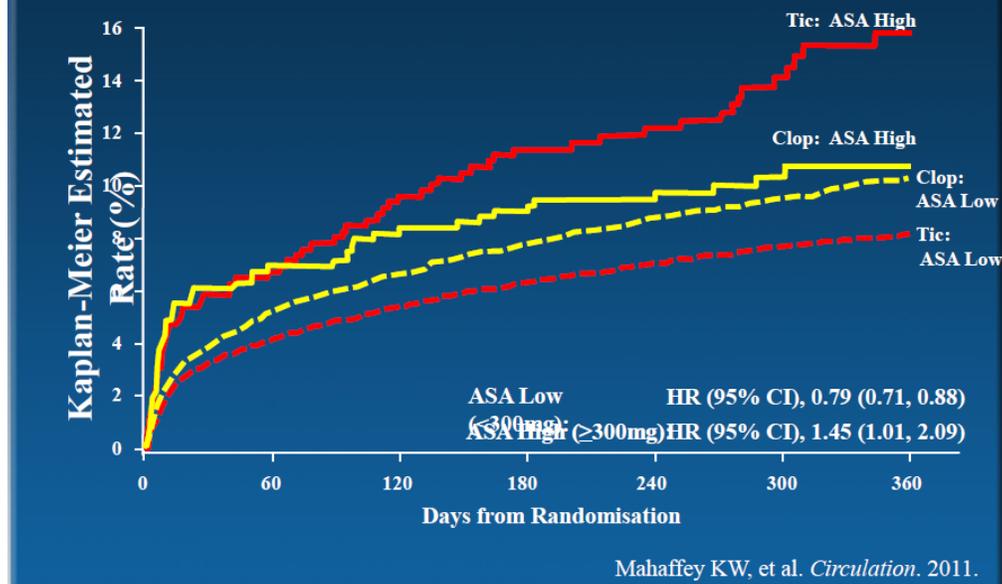


FIGURE 1. The rate of major and total bleeding complications. *p <.005.

More recently from PLATO, low dose aspirin cotherapy with ticagrelor was associated with fewer primary efficacy outcome events (CV death, MI or stroke) as compared to high dose aspirin cotherapy, as seen in the figure below:

PLATO: Primary Efficacy Outcome by ASA Maintenance Dose



Most importantly and most definitively, however, was the randomized, prospective comparison of high-dose versus low-dose aspirin that was performed in OASIS-7, a contemporary mega-trial of antiplatelet therapy in NSTEMI patients with the following design elements and outcomes:

- A 2-by-2 factorial, DB study of 25,000 patients with ACS with planned invasive strategy randomized to either high-dose clopidogrel (a 600-mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg daily thereafter) and a loading dose of 325 mg on day one and then either high-dose aspirin (300 to 325 mg daily) or low-dose aspirin (75 to 100 mg daily)
- Primary outcome of CV death, MI, or stroke at 30 days
- 99+% underwent coronary angiography (so clearly there was intent to revascularize the subjects mechanically but about a third did not get a PCI). Of the ~8000 subjects who did not undergo PCI, 45% had no clinically significant coronary artery disease, 24% underwent CABG, and 31% were not candidates for any type of revascularization.
- Efficacy outcomes were indistinguishable for the high vs. low aspirin doses: 4.2% vs. 4.4% for primary efficacy outcome (hazard ratio, 0.97; 95% CI, 0.86 to 1.09; P=0.61)
- A study-specific definition of major bleeding was used per table 3 below from the OASIS-7 publication, but TIMI criteria for major bleeding were also reported

- Major bleeding rates (study definition) for high and low aspirin doses were the same: 2.3% vs. 2.3% (hazard ratio, 0.99; 95% CI, 0.84 to 1.17; P=0.90), however there was more minor bleeding for the high versus the low aspirin doses: 5.0% vs. 4.4% (hazard ratio, 1.13; 95% CI, 1.00 to 1.27; P=0.04)
- The rate of GI bleeding was higher for the high vs. low aspirin doses: (47 patients [0.4%] vs. 29 patients [0.2%], P = 0.04).
- The important outcomes of this trial, by aspirin dose group, are shown in the table below (from the CURRENT–OASIS 7 Investigators. N Engl J Med 2010;363:930-942):

Table 3. Major Outcomes at 30 Days, According to Dose of Aspirin.*

Outcome	Higher Dose (N=12,507) number (percent)	Lower Dose (N=12,579) number (percent)	Hazard Ratio (95% CI)	P Value
Primary outcome: death from cardiovascular causes, myocardial infarction, or stroke	530 (4.2)	549 (4.4)	0.97 (0.86–1.09)	0.61
Secondary outcomes				
Death from cardiovascular causes, myocardial infarction, stroke, or recurrent ischemia	563 (4.5)	608 (4.8)	0.93 (0.83–1.04)	0.21
Death from cardiovascular causes	259 (2.1)	289 (2.3)	0.90 (0.76–1.06)	0.22
Myocardial infarction	253 (2.0)	261 (2.1)	0.97 (0.82–1.16)	0.76
Stroke	70 (0.6)	59 (0.5)	1.19 (0.84–1.68)	0.32
Recurrent ischemia	41 (0.3)	65 (0.5)	0.63 (0.43–0.94)	0.02
Death from any cause	273 (2.2)	314 (2.5)	0.87 (0.74–1.03)	0.10
Bleeding				
Major				
Study criteria	282 (2.3)	286 (2.3)	0.99 (0.84–1.17)	0.90
Requiring red-cell transfusion ≥2 units	239 (1.9)	238 (1.9)	1.01 (0.84–1.21)	0.93
CABG-related	111 (0.9)	126 (1.0)	0.88 (0.68–1.14)	0.34
Severe	216 (1.7)	215 (1.7)	1.01 (0.84–1.22)	0.93
Leading to decrease in hemoglobin level ≥5 g/dl	115 (0.9)	122 (1.0)	0.95 (0.73–1.22)	0.67
Symptomatic intracranial	6 (0.05)	4 (0.03)	1.51 (0.42–5.33)	0.53
Fatal	16 (0.1)	15 (0.1)	1.07 (0.53–2.17)	0.85
TIMI criteria	197 (1.6)	181 (1.4)	1.09 (0.89–1.34)	0.39
Minor	618 (5.0)	551 (4.4)	1.13 (1.00–1.27)	0.04

* The percentages are Kaplan–Meier estimates of the event rates at 30 days. CABG denotes coronary-artery bypass grafting, and TIMI Thrombolysis in Myocardial Infarction.

We think this is likely to be the best and last data we will get on this subject. If there is no clear advantage of high dose aspirin in the setting which most clearly requires effective platelet inhibition, then it is very unlikely there is an advantage in other settings. We do not make much of the similarity of the bleeding outcomes; we know that over a longer period time the bleeding outcomes for the two doses are different. Fuster in the accompanying editorial states:

“First, when the dosing regimens of aspirin were evaluated on a risk–benefit basis, the lower-dose regimen emerged the winner, with equivalent efficacy but lower rates of minor bleeding than the higher-dose regimen. The lower rate of minor bleeding may not impress clinical trialists, but it certainly has relevance for our patients and their clinicians. It is time for the proponents of higher-dose aspirin to concede defeat and modify clinical practice.”

In his editorial, Fuster also recommended that all ACS patients receive low dose aspirin (75 - 100 mg/day) from day 2 onward following ACS regardless of whether they were treated with PCI, CABG, or medical therapy.

DCRP Conclusions for Question 2:

- The 10-15% lower exposure to aspirin for PA32540 tablets compared to Ecotrin® 325 mg is not clinically meaningful as this change in aspirin plasma exposures at 325 mg does not affect platelet inhibition.
- While there appears to be no incremental benefit in chronic administration of doses of ASA above 100 mg, it is generally accepted that there is a dose-related increase in bleeding – particularly gastrointestinal bleeding (nominally significant increase in GI bleeding demonstrated in both CURE and OASIS-7)
- The data about the relationship between aspirin dose and bleeding are persuasive despite essentially all of it coming from subjects who have not been randomized to the dose of aspirin (OASIS-7 randomized the aspirin dose)
- Finally, it should be noted that the patients for whom Pozen’s ASA+omeprazole will be indicated is a subpopulation at higher risk for adverse gastrointestinal events than the population for whom ASA is indicated in the professional label, 21CFR 341.80. The draft label submitted by Pozen states its product is: “indicated for patients who require aspirin ... (b) (4) in patients at risk for developing aspirin-associated gastric ulcers.” Furthermore, not all patients on ASA for prevention of CV disease were eligible to enroll in the two pivotal trials but rather the eligibility criteria allowed enrollment only of a subpopulation at higher risk of gastric ulcers.
- Given the lack of a dose-related increase in efficacy and a dose-related increase in harm, it seems to us that patients at sufficient risk for gastric ulceration to require chronic administration of a PPI should not be administered 325 mg of aspirin.

Q.3 Please provide a review of the proposed PLR labeling specific to the ASA component. If possible, DGIEP requests a .pdf of the proposed labeling with proposed revisions made as tracked changes.

A tracked changes version of the label with edits from DCaRP will be sent to DGIEP. Based on our response to the question above, we will recommend that you approve only the dose of ASA + omeprazole containing 81 mg of ASA. Also, because the ASA in ASA+omeprazole is enteric coated, the label should state that ASA+omeprazole is not indicated for use on day 1 of an acute myocardial infarction or on the day of PCI in patients not chronically taking ASA.

Q.4 Review the two platelet aggregation studies, PA32540-110 and PA32540-111 and provide recommendations on whether or what information from these studies should be included in the label. Note that the proposed label contains reference to platelet aggregation studies in Section 7.14 and Section 12.2.

Studies PA32540-110 and PA32540-111 have been reviewed. Based on the results, it is not possible to rule out an interaction between the omeprazole component of PA32540 and clopidogrel 75 mg either administered concomitantly or when separated by 10 h. The individual study reviews are provided in the Appendix.

APPENDIX

STUDY NO: PA32540-110

TITLE

A randomized, open-label, crossover study to evaluate the inhibitory effect of clopidogrel plus EC aspirin (325 mg) and clopidogrel plus PA32540 on platelet aggregation in healthy volunteers

BACKGROUND

Clopidogrel is an inactive prodrug requiring metabolism by cytochrome P450 isozymes, importantly CYP2C19, to form its active metabolite. The active metabolite acts by irreversibly binding to the P₂Y₁₂ receptor of platelets thereby inhibiting platelet aggregation. Clopidogrel is often co-administered with proton pump inhibitors (PPIs). Some PPIs are inhibitors of CYP2C19. By inhibiting CYP2C19, PPIs may decrease the formation of the clopidogrel active metabolite, thereby attenuating the desired effect of inhibiting platelet aggregation.

In the current study, the applicant aims to evaluate the pharmacodynamic interaction potential of the omeprazole component of PA32540 when co-administered with clopidogrel, concomitantly and at least 10 h apart.

OBJECTIVES

Primary:

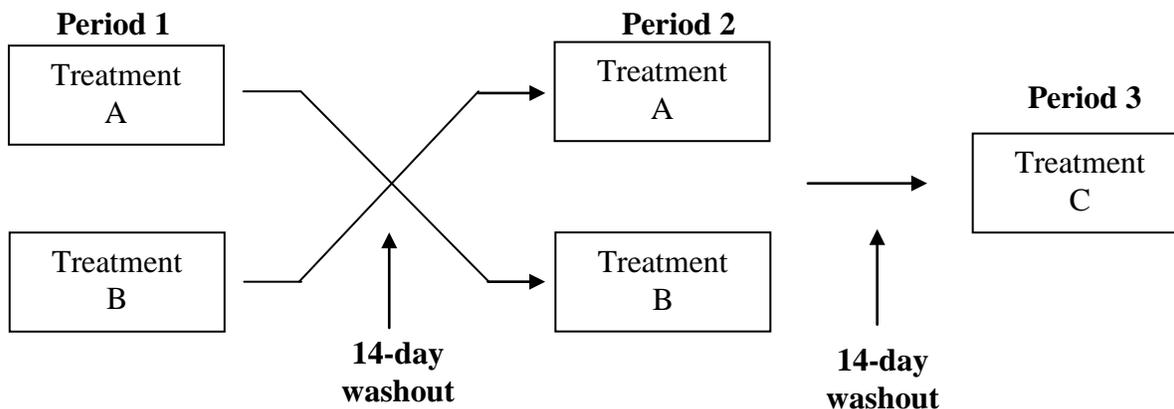
To compare inhibition of platelet aggregation induced by adenosine diphosphate (ADP) 20 µM between clopidogrel + EC aspirin 325 mg and clopidogrel + PA32540 treatment arms taken concomitantly and at least 10 h apart.

Secondary:

To compare inhibition of platelet aggregation between clopidogrel + EC aspirin 325 mg and clopidogrel + PA32540 treatment arms using – (i) ADP 5 µM, and (ii) arachidonic acid (AA) 2 mM as agonists; (iii) VerifyNow P₂Y₁₂ assay, (iv) VerifyNow aspirin assay, and (v) vasodilator stimulated phosphoprotein (VASP) phosphorylation assay.

STUDY DESIGN

A randomized, open-label, single-center, partial crossover study in healthy volunteers



Treatment arms:

A = Clopidogrel 300 mg + EC aspirin 325 mg on Day 1; clopidogrel 75 mg + EC aspirin 325 mg on Days 2-7

B = Clopidogrel 300 mg + PA32540 on Day 1; clopidogrel 75 mg + PA32540 on Days 2-7

C = PA32540 (morning) + clopidogrel 300 mg (afternoon) on Day 1; PA32540 (morning) + clopidogrel 75 mg (afternoon) on Days 2-7

Test products:

- EC aspirin = Ecotrin[®]
- Clopidogrel = Plavix[®]
- PA32540 = FDC of EC aspirin 325 mg with an outer coating of immediate release omeprazole 40 mg

Approximately 30 healthy adults were planned, enrolled, randomized and treated for the first two treatment periods and 28 of the same subjects were treated for the added third treatment arm.

Subjects were healthy adult males or non-lactating, non-pregnant females at least 40 years of age with a body mass index of 19 to 30 kg/m². Subjects were required to have \geq 70% platelet aggregation function at screening and could not have taken any antiplatelet drug or more than two 325 mg doses of aspirin (or other NSAID) within 2 weeks of the screening visit.

Reviewer's comment: Omeprazole is a mechanism based inhibitor of CYP2C19.

Therefore, maximal inhibition effects following the first dose of clopidogrel can only be observed upon pre-treatment with omeprazole which is not how the current study was designed.

PHARMACOKINETICS

No pharmacokinetic evaluation was performed.

Reviewer's comment: *Drug interactions between clopidogrel and PPIs have been primarily addressed by pharmacokinetic results i.e., exposure to the active metabolite of clopidogrel, with platelet inhibition data as supportive evidence.*

PHARMACODYNAMICS

Blood samples were obtained for platelet aggregation evaluation during the screening phase, prior to dosing on Day 1, approximately 24 h after Day 1 dosing and just prior to dosing on Day 2, and one hour after dosing on Day 7 of each period.

Platelet aggregation (PA) in response to clopidogrel and aspirin was primarily assessed by light transmittance aggregometry using ADP and AA, respectively as agonists. In addition, platelet function was also evaluated by VASP phosphorylation assay (receptor reactivity ratio, RRR), VerifyNow P₂Y₁₂ (P₂Y₁₂ reactivity unit, PRU) and VerifyNow aspirin (aspirin reactivity unit, ARU) assay.

Inhibition of platelet aggregation (IPA), % is calculated as in Eqn. (1). Inhibition of platelet function by other methodologies is also calculated similarly, but, substituting RRR, PRU and ARU, respectively for PA.

$$\text{IPA, \%} = [\text{PA}_{\text{bsln}} - \text{PA}_{\text{end}}] / \text{PA}_{\text{bsln}} * 100 \text{ ----- Eqn. (1)}$$

CYP2C19 GENOTYPING

No genotyping to determine CYP2C19 loss-of-function allele carrier status was performed.

SAMPLE SIZE DETERMINATION

The sample size was derived using a 2.5% one-sided test with 90% power to reject the null hypothesis that PA32540 + clopidogrel is inferior to EC aspirin 325 mg + clopidogrel at a non-inferiority margin of 10 units. The sample size and power calculations were made under the assumption that non-inferiority was to be tested with the expectation that the difference between PA32540 + clopidogrel and EC aspirin 325 mg + clopidogrel would be zero, that EC aspirin 325 mg + clopidogrel would have a mean IPA of 40 with a standard deviation of 12. The sponsor claims that the sample size also provided sufficient power to test the non-inferiority between sequentially administered PA32540 + clopidogrel (10 h apart) and EC aspirin 325 mg + clopidogrel.

Reviewer's comment: *A non-inferiority margin of 10% in platelet inhibition is not interpretable in terms of how it translates to clinical outcomes.*

STATISTICAL ANALYSIS

A mixed-effect ANOVA model on the pharmacodynamic parameter (e.g., IPA %) was fitted with sequence, period and treatment as fixed effects and subjects within sequence as random effect. Two-sided 95% CI for the least square mean difference of the pharmacodynamic metric between PA32540 + clopidogrel and EC aspirin 325 mg + clopidogrel was calculated. In addition, paired mean differences and 95% CI were calculated between EC aspirin 325 mg + clopidogrel and sequentially administered PA32540 + clopidogrel (10 h apart). Non-inferiority was established if the upper bound of a two-sided 95% CI for LS mean difference between the two treatment arms in comparison was less than or equal to 10%.

RESULTS

Study subjects and disposition:

- All 30 randomized subjects completed the two treatment periods and therefore were included in the intent to treat (ITT) and safety populations. A total of 28 subjects completed the third sequential treatment period. Two subjects (7%) were prematurely withdrawn due to personal reasons.

Pharmacodynamics:

- Concomitant administration of PA32540 with clopidogrel 75 mg reduced the mean IPA by 15.1% and 16.6% relative to control on Day 7 with ADP 5 μ M and 20 μ M, respectively as agonist (Table 1). When PA32540 and clopidogrel 75 mg were administered 10 h apart, the mean IPA was reduced by 9.7% and 13.8% on Day 7 with ADP 5 μ M and 20 μ M, respectively as agonist (Table 1).
- Other platelet function assays also showed significant inhibition of platelet function when PA32540 was administered with clopidogrel 75 mg concomitantly or 10 h apart relative to EC aspirin 325 mg + clopidogrel on Day 7 (Table 2).
- The antiplatelet response measured after stimulation by AA is similar across both treatment arms.

Reviewer's comments:

- *Platelet aggregation results following Day 1 is not discussed further in this review as it may represent incomplete CYP2C19 inhibition. It is well known that omeprazole is a mechanism based inhibitor of CYP2C19 requiring pre-treatment to generate metabolites which inhibits the enzyme in an irreversible fashion. Therefore, maximal inhibition effects following the first dose of clopidogrel can only be observed upon pre-treatment with omeprazole which is not how the current study was designed. Studies performed earlier (NDA 20839; DARRTS date: 11/02/2009) where delayed release omeprazole 80 mg was administered for 5 days prior to administration of the loading dose of clopidogrel*

showed a 45% decrease in the plasma exposure to clopidogrel active metabolite with corresponding decreases in IPA.

- As mentioned earlier, relationship between platelet inhibition and clinical outcomes are poorly understood. A non-inferiority margin of 10% in platelet inhibition is non-interpretable in terms of how it translates to clinical outcomes. Due to this reason, the Division of Cardio-Renal Products has always used 80-125% bioequivalence limits to the plasma exposure of clopidogrel active metabolite as the primary basis to address drug interactions between clopidogrel and PPIs.

Safety:

- There were no deaths or other serious adverse events in the study and no withdrawals due to adverse events.

Table 1: Analysis of inhibition of platelet aggregation between treatment groups on Day 7 using ADP and AA as agonist

CROSSOVER PERIOD				
Assay	LS Mean (SE)		LS Mean Difference (95% CI)	% decrease relative to control
	A (N=30)	B (N=30)	A vs B	
ADP 20 µM	43.96 (2.31)	36.65 (2.31)	7.30 (1.44, 13.2)	16.6
ADP 5 µM	53.98 (2.49)	45.85 (2.49)	8.13 (2.53, 13.7)	15.1
AA 2 mM	91.15 (3.16)	91.41 (3.16)	-0.26 (-0.93, 0.41)	--
FIXED PERIOD				
Assay	Mean (SD)		Mean Difference (95% CI)	% decrease relative to control
	A (N=28)	C (N=28)	A vs C	
ADP 20 µM	44.39 (13.7)	39.97 (11.9)	4.41 (-0.78, 9.61)	9.96
ADP 5 µM	54.09 (15.1)	46.61 (14.1)	7.48 (0.89, 14.1)	13.8

Table 2: Analysis of inhibition of platelet function between treatment groups on Day 7 using RRR, PRU and ARU as agonist

CROSSOVER PERIOD				
Assay	LS Mean (SE)		LS Mean Difference (95% CI)	% decrease relative to control
	A (N=30)	B (N=30)	A vs B	
RRR	52.77 (3.61)	34.45 (3.61)	18.32 (10.7, 25.9)	34.7
PRU	56.12 (2.96)	32.75 (2.96)	23.37 (17.9, 28.8)	41.6
ARU	34.50 (1.73)	36.43 (1.73)	-1.93 (-5.97, 2.11)	--

FIXED PERIOD				
Assay	Mean (SD)		Mean Difference (95% CI)	% decrease relative to control
	A (N=28)	C (N=28)	A vs C	
RRR	51.85 (18.43)	41.73 (20.02)	10.12 (3.56, 16.7)	19.5
PRU	56.46 (16.92)	40.61 (18.8)	15.85 (9.87, 21.8)	28.1

CONCLUSION

Pharmacokinetics of the clopidogrel active metabolite was not characterized in this study. There is a decrease in platelet inhibition when clopidogrel is administered concomitantly with PA32540 relative to clopidogrel + EC aspirin 325 mg. Separation in the administration of PA32540 and clopidogrel by 10 h shows a relative increase in platelet inhibition compared to concomitant administration following the use of ADP 20 μ M as agonist, however, with no internal consistency with results using ADP 5 μ M. From an earlier study (NDA 20839, DARRTS date: 11/02/2009) we know that the platelet inhibition results are no different when clopidogrel is administered with delayed release omeprazole 80 mg concomitantly or separated by 12 h, due to the mechanistic irreversible inhibition of CYP2C19 by omeprazole. From another study (IND (b) (4) DARRTS date: 08/20/2012) which evaluated concomitant administration of clopidogrel 75 mg with delayed release omeprazole 20 mg, the mean AUC_{0-t} of clopidogrel active metabolite was decreased by 18% with the 90% CIs of the geometric mean ratio not contained within the bioequivalence limits of 80-125%. In the light of these findings and the absence of pharmacokinetic data, we recommend avoid use of PA32540 with clopidogrel when administered concomitantly or 10 h apart.

STUDY NO: PA32540-111

TITLE

A randomized, open-label, crossover study to evaluate the inhibitory effect of clopidogrel, EC aspirin 81 mg and EC omeprazole 40 mg all dosed concomitantly and PA32540 and clopidogrel dosed separately on platelet aggregation in healthy volunteers

BACKGROUND

Study PA32540-110 evaluated the pharmacodynamic interaction between EC aspirin 325 mg + clopidogrel and PA32540 + clopidogrel when dosed concomitantly and 10 h apart. The current study was conducted to provide further *ex vivo* data on the platelet inhibitory effect of PA32540 + clopidogrel when dosed separately (10 h apart) as compared to concomitant administration of EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel.

OBJECTIVES

Primary:

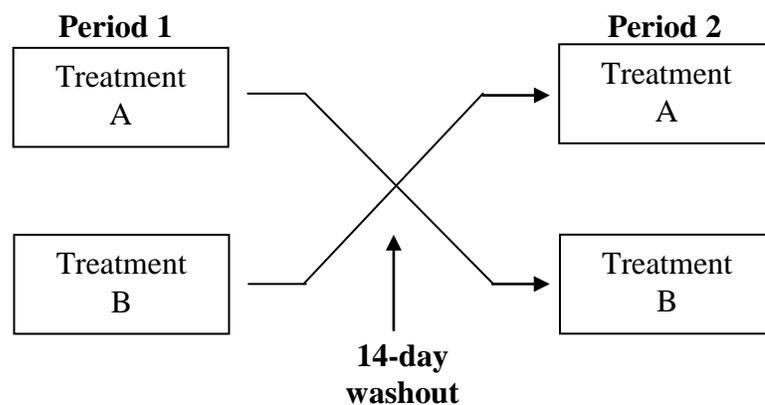
To evaluate ADP-induced platelet aggregation following administration of clopidogrel, EC aspirin 81 mg and EC omeprazole 40 mg all dosed concomitantly *vs* PA32540 and clopidogrel dosed separately.

Secondary:

To evaluate AA-induced platelet aggregation following administration of clopidogrel, EC aspirin 81 mg and EC omeprazole 40 mg all dosed concomitantly *vs* PA32540 and clopidogrel dosed separately.

STUDY DESIGN

A randomized, open-label, single-center, two-way crossover study in healthy volunteers



Treatment arms:

A = PA32540 (morning) + clopidogrel 300 mg (afternoon) on Day 1; PA32540 (morning) + clopidogrel 75 mg (afternoon) on Days 2-7

B = EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel 300 mg on Day 1; EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel 75 mg on Days 2-7

Test products:

- EC aspirin = Bayer[®]
- Clopidogrel = Plavix[®]
- EC omeprazole = Prilosec[®]
- PA32540 = FDC of EC aspirin 325 mg with an outer coating of immediate release omeprazole 40 mg

Approximately 30 healthy adult volunteers were planned, enrolled and randomized to the two treatment groups. Twenty nine subjects completed treatment A and 30 subjects completed treatment B.

Subjects were healthy adult males or non-lactating, non-pregnant females at least 40 years of age with a body mass index of 19 to 30 kg/m². Subjects were required to have ≥ 70% platelet aggregation function at screening and could not have taken any antiplatelet drug or more than two 325 mg doses of aspirin (or other NSAID) within 2 weeks of the screening visit.

PHARMACOKINETICS

No pharmacokinetic evaluation was performed.

Reviewer's comment: *Drug interactions between clopidogrel and PPIs have been primarily addressed by pharmacokinetic results i.e., exposure to the active metabolite of clopidogrel, with platelet inhibition data as supportive evidence.*

PHARMACODYNAMICS

Blood samples were obtained for platelet aggregation evaluation during the screening phase and prior to dosing on Day 1. On Day 7, subjects receiving treatment A had one blood sample drawn for AA-induced platelet aggregation evaluation 2 h after morning dosing of PA32540 and 2 additional blood samples taken for ADP-induced platelet aggregation evaluation 2 h after the evening dose of clopidogrel. Subjects receiving treatment B had blood samples drawn 2 h after their concomitant morning dose, one sample for AA-induced and 2 samples for ADP-induced platelet aggregation evaluation.

Platelet aggregation (PA) in response to clopidogrel and aspirin was primarily assessed by light transmittance aggregometry. Inhibition of platelet aggregation (IPA), % is calculated as in Eqn. (1).

$$\text{IPA, \%} = [\text{PA}_{\text{bsln}} - \text{PA}_{\text{end}}] / \text{PA}_{\text{bsln}} * 100 \text{ ----- Eqn. (1)}$$

CYP2C19 GENOTYPING

No genotyping to determine CYP2C19 loss-of-function allele carrier status was performed.

SAMPLE SIZE DETERMINATION

The sample size was derived using a 5% two-sided test with 90% power to detect a mean difference of 10% in IPA between PA32540 + clopidogrel dosed separately and EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel dosed concomitantly assuming that the mean IPA of PA32540 + clopidogrel dosed separately is 40 and the standard deviation of treatment differences is 14.

STATISTICAL ANALYSIS

A mixed-effect ANCOVA model on IPA % was fitted with sequence, period and treatment as fixed effects and subjects within sequence as random effect and baseline platelet aggregation as a covariate. Two-sided 95% CI for the least square mean difference between the treatment arms was calculated.

RESULTS

Study subjects and disposition:

- Thirty subjects completed treatment A and 29 subjects completed treatment B. One subject (3%) discontinued early due to an adverse event.

Pharmacodynamics:

- There was an 18.5% increase in mean IPA-induced by ADP 20 μ M when PA32540 + clopidogrel was administered 10 h apart when compared to EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel administered concomitantly. No significant differences in mean IPA-induced by AA 2 mM were found between the treatment arms.

Reviewer's comments:

- *Though there was a modest increase in mean IPA-induced by ADP 20 μ M with administration of PA32540 + clopidogrel 10 h apart, we do not know the platelet inhibitory effect relative to clopidogrel administered alone. In other words, this study lacks an appropriate control arm.*
- *As mentioned earlier, relationship between platelet inhibition and clinical outcomes are poorly understood. The Division of Cardio-Renal Products has always used 80-125% bioequivalence limits to the plasma exposure of clopidogrel active metabolite as the primary basis to address drug interactions between clopidogrel and PPIs.*

Safety:

There were no deaths or other serious adverse events in the study and no withdrawals due to adverse events.

Table 2: Analysis of inhibition of platelet aggregation between treatment groups on Day 7

Assay	LS Mean (SE)		LS Mean Difference (95% CI)	% increase relative to control
	A (N=30)	B (N=30)	A vs B	
ADP 20 μ M	46.50 (3.55)	39.25 (3.53)	7.24 (2.57, 11.9)	18.5
AA 2 mM	91.86 (1.27)	92.06 (1.25)	-0.21 (-3.61, 3.19)	--

CONCLUSION

This study lacks an appropriate control arm. The comparison of importance is the platelet inhibitory effects of PA32540 + clopidogrel administered 10 h apart relative to EC aspirin + clopidogrel. Based on the results from the previous study PA32540-110, we know that there is a decrease in mean IPA by approximately 10-14% when PA32540 is administered with clopidogrel separated by 10 h relative to clopidogrel + EC aspirin 325 mg. As the relationship between platelet inhibition and clinical outcomes is poorly understood, this interaction cannot be addressed in the absence of pharmacokinetic data.

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/s/

PRESTON M DUNNMON
01/16/2014

SUDHARSHAN HARIHARAN
01/16/2014

RAJANIKANTH MADABUSHI
01/16/2014

NORMAN L STOCKBRIDGE
01/16/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Donna Snyder, MD
Pediatric and Maternal Health Staff (PMHS)

Through: Hari Cheryl Sachs, MD, Team Leader, Pediatrics Team
Jeanine Best, MSN, RN, PNP, Team Leader, Maternal Health Team
Lynne Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff (PMHS)

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Yosprala® (aspirin/omeprazole)
Two proposed dosages in tablet formulation:
-81 mg delayed release aspirin/40 mg immediate release omeprazole or
-325 mg delayed release aspirin/40 mg immediate release omeprazole

NDA: 205103

Re: Pediatric Review Committee (PeRC) preparation assistance and input on labeling for the Pediatric Use, Pregnancy and Nursing Mothers sections of labeling.

Sponsor: Pozen, Inc.

Proposed Indication: (b) (4)



Consult Request:

"Pediatric: The reason for this consult is to invite the Pediatric team to attend meetings regarding this NDA and assist in the labeling review and PeRC preparation as needed.

Maternal Health: The reason for this consult is to invite the Maternal Health team to attend meetings and assist in the labeling review pertaining to this NDA and offer any assistance as necessary."

Materials Reviewed:

- Proposed Yosprala® (aspirin/omeprazole) labeling dated April 30, 2013
- Sponsor's pediatric waiver request submitted to the NDA
- PeRC Pediatric Research Equity Act (PREA) Subcommittee Meeting Minutes dated September 25, 2013, (DARRTS Reference ID: 3385395)
- Prilosec® (omeprazole) approved labeling, May 15, 2013
- Aggrenox® (aspirin/dipyridamole) labeling, September 7, 2012.
- PMHS- Maternal Health Team (MHT) consult reviews on Prilosec®, NDA 19801 dated April 15, 2013, (DARRTS Reference ID: 3293025) 19,2013)
- PMHS-MHT consult reviews on Nexium®, NDA 21689 dated July 10, 2013, (DARRTS Reference ID: 3338852)
- PMHS -Pediatric consult review on esomeprazole or omeprazole containing prescription proton pump inhibitors dated October 23, 2013, (DARRTS Reference ID: 3394820)
- REPRORISK and LactMed database review for aspirin information

Background:

Pozen, Inc. submitted a 505(b)(2) application on April 25, 2013 for a combination product that contains delayed release aspirin [acetylsalicylic acid (ASA)] and immediate release omeprazole. Prilosec® and Ecotrin® serve as the reference listed drugs (RLD) for the application. The combination product is produced with two strengths of ASA, 325 mg and 81 mg and one strength of omeprazole at 40 mg. The proposed indication is for secondary prevention of cardiovascular and cerebrovascular events in patients that are at risk of developing aspirin associated gastric ulcers.

Acetylsalicylic acid (ASA) is an anti-platelet agent that is commonly used to prevent subsequent cardiovascular and cerebrovascular events in patients who have had a

previous event.¹ Omeprazole is a proton pump inhibitor (PPI) that belongs to a class of antisecretory compounds, the substituted benzimidazoles, which suppress gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase enzyme system in the gastric parietal cell.² Use of a PPI in combination with ASA may reduce the risk of upper GI bleeding that may occur with chronic ASA use.³

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff (PMHS) to review the Pregnancy, Nursing Mothers, and Pediatric Use subsections in Yosprala® (aspirin/omeprazole) labeling and to help DGIEP prepare for the Pediatric Review Committee (PeRC) meeting.

Pediatric Review:

Under the Pediatric Research Equity Act (PREA), all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must include a pediatric assessment that is adequate to assess the safety and effectiveness of the product and to support dosing and administration for all relevant pediatric populations, unless a deferral or waiver are granted by the Agency. Yosprala® triggers PREA as both a new active ingredient and a new indication. The sponsor requested a full waiver of studies.

The criteria for a full or partial waiver under the Pediatric Research and Equity Act (PREA) are the following:

1. Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).
2. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information must be included in labeling.
3. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

In addition, a partial waiver can be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

¹ Hennekens, C and Dalen, J. Aspirin in the Treatment and Prevention of Cardiovascular Disease: Past and Current Perspectives and Future Directions. *The American Journal of Medicine*: 2013. 126; 373-378

² Prilosec® (omeprazole) approved labeling, May 15, 2013.

³ Saini, D. et al. Cost-effectiveness of Proton Pump Inhibitor Cotherapy in Patients Taking Long-term, Low-Dose Aspirin for Secondary Cardiovascular Prevention. *Arch Intern Med*. 2008;168(15):1684-1690.

The sponsor submitted a request for a full waiver of pediatric studies on the grounds that necessary studies are impossible and highly impractical and on the grounds that the product would be unsafe for use in the pediatric population. Studies would be impossible or highly impractical because of the very low prevalence of pediatric patients with myocardial infarction, stroke, chronic stable angina or transient ischemia of the brain who would also be at risk for aspirin associated ulcers. Additionally, studies would be unsafe in some pediatric populations because of the association between aspirin and Reye's syndrome. The current monograph for aspirin (21 CFR 343.80) includes a contraindication that aspirin should not be used in pediatric patients with viral infections because of the risk of Reye's Syndrome. Since Yosprala® may be used chronically as a preventative agent, pediatric patients may develop intercurrent viral illnesses while on the product and be at risk for Reye's Syndrome.

The PeRC met on September 25, 2013 and agreed to the full waiver on the grounds that studies would be impossible or highly impractical "because the proposed indication in the pediatric population is rare, therefore the incidence of aspirin associated gastric ulcers would also expected to be rare."⁴

Pediatric Use Labeling:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

Since the approval of Prilosec® (omeprazole) the RLD, FDA became aware of data indicating that use of esomeprazole, a related product, in pregnancy may cause fetal harm with changes in bone morphology and physeal dysplasia in pre- and postnatal developmental toxicity studies in rats. Adverse effects were also seen on maternal bone in pregnant and lactating rats. DGIEP is invoking FDAAA to request safety labeling changes in the Pregnancy, Nursing Mothers and Pediatric Use section for all esomeprazole and omeprazole products based on this animal data. Labeling recommendations for Yosprala® (aspirin/omeprazole) include the recent recommendations based on this animal data.⁵

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

⁴ PeRC Pediatric Research Equity Act (PREA) Subcommittee Meeting Minutes dated September 25, 2013, (DARRTS Reference ID: 3385395)

⁵ PMHS Consult review by A. Karesh dated October 23, 2103, DARRTS Reference ID: 3394820

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

/s/

DONNA L SNYDER
12/20/2013

HARI C SACHS
12/20/2013
I agree with the pediatric labeling recommendations .

LYNNE P YAO
12/22/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: December 11, 2013

TO: Anissa Davis, M.P.H., Project Manager
Zana Marks, M.D., Medical Officer

FROM: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch

THROUGH: Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205-103

APPLICANT: Pozen, Inc.

DRUG: (b) (4) (aspirin/omeprazole)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Secondary prevention of cardio and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers

CONSULTATION REQUEST DATE: May 20, 2013
INSPECTION SUMMARY GOAL DATE: December 20, 2013
DIVISION ACTION GOAL DATE: January 24, 2014
PDUFA DATE: January 24, 2014

I. BACKGROUND:

The sponsor, POZEN, Inc. submitted an NDA for the indication of secondary prevention of cardio-and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers. Data from two identical protocols, PA32540-301 and PA32540-302, both entitled “A 6-Month, Phase 3, Randomized, Double-Blind, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric Coated Aspirin 325 mg in subjects Who Are at Risk for Developing Aspirin-Associated Ulcers” were submitted in support of the NDA.

The protective effect of low-dose aspirin (≤ 325 mg/day) against serious cardiac and cerebrovascular events are well established. At the same time aspirin can be associated with considerable gastro-intestinal damage even with the use of enteric-coated or buffered aspirin. The studies submitted to the NDA used a proprietary tablet consisting of enteric-coated 325 mg aspirin and omeprazole in the outer layer (b) (4). The sponsor claimed (u) (4).

Study Objectives:

- To demonstrate that the study drug (PA32540) causes fewer gastric ulcers in subjects at risk for developing aspirin-associated gastric ulcers compared to enteric coated aspirin 325 mg.
- To demonstrate that PA32540 causes fewer gastric and/or duodenal ulcers in subjects at risk for developing aspirin-associated ulcers compared to enteric coated aspirin 325 mg.
- To compare between treatments, the proportion of subjects with “Treatment Successes” (defined as those subjects without gastric ulcers and without UGI (upper gastrointestinal) adverse events leading to discontinuation.
- To compare between treatments, the proportion of subjects discontinuing the study due to UGI adverse events
- To compare between treatments, the proportion of subjects with heartburn resolution, defined as the answer “NONE” on the heartburn assessment question.
- To evaluate the overall safety of PA32540 (b) (4) as compared to enteric coated (EC) aspirin 325 mg

Sites were selected because they had the largest number of enrollees per study (Study PA3245-301 and Study PA3245-302). Many sites had less than 15 subjects enrolled.

II. RESULTS (by Site):

Name of CI, Location and Site #	Protocol # and # of Subjects	Inspection Date	Final Classification
Sabine Hazan-Steinberg, M.D. Ventura Clinical Trials 1746 S. Victoria Ave., Suite 230 Ventura, CA 93003 Site 0776	PA32540-301 31 Subjects	July 10-15, 2013	NAI
Neal Secrist, M.D. Professional Research Network of Kansas 345 Riverview Street, Suite 400 Wichita, KS 67203 Site 0671	PA32540-302 22 Subjects	July 15-18, 2013	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Sabine Hazan-Steinberg, M.D.-

1746 S. Victoria Ave, Ventura, CA 93003

- a. What was inspected:** At this site, 39 subjects were screened, 8 subjects were screen failures, 31 were randomized, and 30 subjects completed the study. The field investigator reviewed the records of 15 subjects. The field investigator reviewed inclusion/exclusion criteria, informed consents, drug accountability records, primary efficacy endpoints, monitoring reports and adverse reactions.
- b. General observations/commentary:** The field investigator did not report any violations of federal regulations at this site
- c. Assessment of data integrity:** The data collected from this site can be used in support of the NDA

2. Neal Secrist, M.D.

345 Riverview Street, Suite 400, Wichita, KS 67203

- a. What was inspected:** At this site, 26 subjects were screened, 4 subjects were screen failures and 22 were enrolled. Four subjects were withdrawn and 18 completed the study. The field investigator reviewed the records of all 26

subjects. The review included informed consent forms, inclusion/exclusion criteria, drug accountability records, monitoring reports and adverse events. Source documents were compared with the data listings provided and except for minor differences, there were no discrepancies.

- b. General observations/commentary:** No significant regulatory violations were observed.
- c. Assessment of data integrity:** The data generated at this site are reliable, and can be used in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites were selected for inspection for this NDA. The two sites inspected were classified as NAI. The data generated at both sites are acceptable and can be used in support of the NDA.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
12/11/2013

KASSA AYALEW
12/11/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: December 3, 2013

Reviewer: Lisa Vo Khosla, PharmD, M.H.A.
Division of Medication Error Prevention and Analysis

Team Leader Lubna Merchant, M.S., PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Yosprala (Aspirin and Omeprazole)
Delayed-Release Tablets,
325 mg/40 mg and 81 mg/40 mg

Application Type/Number: NDA #205103

Applicant/sponsor: Pozen

OSE RCM #: 2013-993

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review responds to the request from the Division of Gastroenterology and Inborn Errors Products (DGIEP) to evaluate the Applicant's proposed container label, carton labeling, and full prescribing information for Yosprala (Aspirin and Omeprazole) Delayed-Release Tablets, NDA 205103, for areas of vulnerability that could lead to medication errors. DGIEP requested this review as part of their evaluation for NDA 205103.

1.1 PRODUCT INFORMATION

The reference listed drugs, Ecotrin (OTC monograph), was approved November 12, 2010, and Prilosec (NDA 022056), was approved February 9, 2002.

The following product information is provided in the June 5, 2013 submission:

- Active Ingredient: Aspirin and Omeprazole
- Indication of Use: Secondary prevention of cardiovascular and cerebrovascular events in patients at risk of aspirin-induced gastric ulcers
- Route of Administration: Oral
- Dosage Form: Delayed-Release Tablets
- Strength: 325 mg Enteric-coated Aspirin surrounded by 40 mg Immediate-release Omeprazole and 81 mg Enteric-coated Aspirin surrounded by 40 mg immediate-release Omeprazole
- Dose and Frequency: One tablet once daily
- How Supplied: Samples- (b) (4) bottles of 30, 90 (b) (4) tablets (b) (4)
- Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted November 26, 2013 (Appendix B)
- Carton Labeling submitted November 26, 2013 (Appendix C)
- Prescribing Information submitted March 25, 2013

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESSMENT

The Applicant is proposing a combination product that contains aspirin and omeprazole “to ensure that subjects who require chronic aspirin therapy will always receive a preceding PPI dose.” This is the first combination product containing these two ingredients.

We performed a risk assessment of the proposed full prescribing information to identify deficiencies that may lead to medication errors. Additionally, we noted that the statement “Do not split, chew, crush, or dissolve the tablet.” is located on the side panel with other information, which can be overlooked. We provide label and labeling recommendations in section 5 to increase prominence of important information to ensure safe use of the product.

4 CONCLUSIONS

DMEPA concludes that the proposed container label and carton labeling can be improved to increase the readability and prominence of important information on the label. We made recommendations in section 5 that could help promote the safe use of the product and to mitigate any confusion.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Applicant

1) Container Label and Carton Labeling

- a) We recommend revising the presentation of the proprietary name from lowercase (i.e. yosprala) to title case where the letter ‘Y’ is capitalized (i.e. Yosprala) to improve readability of the name.
- b) Relocate the statement “Do not split, chew, crush, or dissolve the tablet.” from the side panel to the principal display panel to highlight the importance of this information.

If you have further questions or need clarifications, please contact Phong Do, OSE project manager, at 301-796-4795.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>

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/s/

LISA V KHOSLA
12/03/2013

LUBNA A MERCHANT
12/03/2013

MEMORANDUM

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

DATE: November 8, 2013

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III

FROM: Xingfang Li, M.D., RAC
Consumer Safety Officer
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
Michael F. Skelly, Ph.D.
Pharmacologist
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 205-103,
(aspirin/omeprazole) Tablets, sponsored by POZEN,
Inc.

At the request of the Division of Gastroenterology and Inborn Errors Products (DGIEP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following studies:

Study Number: PA32540-115
Study Title: "Single-Dose Randomized Crossover Study to Assess the Intrasubject Variability of

Acetylsalicylic Acid from Administration of
an Enteric-Coat (EC) Aspirin Formulation
(Ecotrin® 325 mg) and to Evaluate the
Relative Bioavailability of PA32540 with the
Partial Reference-Replicated 3-Way Design
and the Reference-Scaled Average
Bioequivalence Approach"

Study Number: PA8140-102

Study Title: "Single-Dose, Randomized, 3-Way Crossover
Study to Assess the Bioavailability of
Acetylsalicylic Acid from Administration of
Three Tablets (Dosed Concurrently) of PA8140
Relative to Three tablets of an Enteric-
Coat (EC) Aspirin Formulation (Ecotrin® 81
mg) Using the Partial Reference- Replicated
Design"

The audits included a thorough review of study records,
examination of facilities and equipment, and interviews and
discussions with the firms' management and staff.

Clinical Site:

The audit of the clinical portion was conducted at PPD
Phase-I Clinic, Austin, TX (10/18-10/29/2013 by ORA
Investigator Todd R. Lorenz). Following the inspection at
the clinical site no Form FDA-483 was issued and there were
no significant findings at the site.

Bioanalytical Site:

The audit of the analytical portion was conducted (b) (4)
(b) (4) by ORA investigator (b) (4)
(b) (4) OSI/DBGLPC scientists Xingfang Li and Michael
F. Skelly). Following the inspections at the analytical
site no Form FDA-483 was issued and there were no
significant findings at the site.

Conclusions:

Following the above inspections, we recommend that data for
clinical and analytical portions of studies PA32540-115 and
PA8140-102 are acceptable for further agency review.

Michael F. Skelly, Ph.D.
Pharmacologist

Xingfang Li, M.D., RAC
Consumer Safety Officer

Final Classifications:

Clinical

**NAI: PPD Phase-I Clinic, Austin, TX
FEI 3008374644**

Analytical

NAI: [REDACTED] (b) (4)

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Bonapace/Choi/Mada/Dejernet

OSI/DBGLPC/Haidar/Skelly/Li

OMPT/CDER/OND/ODEIII/DGIEP/Griebel/Lee/Jappard/Davis

ORA/[REDACTED]-DO/HFR-SW150/[REDACTED] (b) (4)

ORA/[REDACTED]-DO/[REDACTED]-IE [REDACTED] (b) (4)

ORA/[REDACTED]-DO/HFR-CE250 [REDACTED] (b) (4)

ORA/[REDACTED]-DO/RIC-RP/HFR-CE2545 [REDACTED] (b) (4)

Draft: XFL 11/7/2013

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ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/ Inspections/BE
Program/Clinical Sites/PPD, Austin, TX

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence &
Good Laboratory Practice Compliance/ Inspections/BE
Program/Analytical Sites/[REDACTED] (b) (4)

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/s/

XINGFANG LI
11/08/2013

MICHAEL F SKELLY
11/08/2013

SAM H HAIDAR
11/14/2013

MEMORANDUM

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

DATE: June 24, 2013

TO: Director, Investigations Branch
Dallas District Office
4040 N. Central Expressway
Suite 300
Dallas, TX 75204

Director, Investigations Branch
Baltimore District Office
6000 Metro Dr., Suite 101
Baltimore, MD 21215

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **CDER High Priority User Fee NDA, Pre-Approval
Data Validation Inspection**, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 205-103
DRUG: Aspirin/omeprazole tablets
SPONSOR: POZEN, Inc.
Chapel Hill, North Carolina

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence studies. **These inspections should be completed prior to November 1, 2013.**

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) to obtain background materials and to schedule the inspections. A DBGLPC scientist may participate in the inspection of the analytical site to provide scientific and technical expertise.

Study #1: PA32540-115

Study Title: "Single-dose randomized crossover study to assess the intrasubject variability of acetylsalicylic acid from administration of an enteric-coat (EC) aspirin formulation (Ecotrin® 325 mg) and to evaluate the relative bioavailability of PA32540 with the partial reference-replicated 3-way design and the reference-scaled average bioequivalence approach"

Study #2: PA8140-102

Study Title: "Single-dose, randomized, 3-way crossover study to assess the bioavailability of acetylsalicylic acid from administration of three tablets (dosed concurrently) of PA8140 relative to three tablets of an enteric-coat (EC) aspirin formulation (Ecotrin® 81 mg) using the partial reference-replicated design"

Clinical Site: PPD Phase I Clinic
7551 Metro Center Drive,
Suite 200
Austin, Texas 78744

Investigator: Aziz L. Laurent, MD

Do not notify the sites of the application number, the studies to be inspected, the drug name, or the study investigators prior to the start of the inspections. The sites will receive this information during the inspection-opening meetings. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

Once the inspections are completed, **please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.**

SECTION A - RESERVE SAMPLES

Because these bioequivalence studies are subject to 21 CFR 320.38 and 320.63, the study site is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing. For additional information, please refer to the final rule for "Retention of

Bioavailability and Bioequivalence Testing Sample¹" and to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples²" referenced below.

During the clinical site inspection, please:

- Verify that the site retained reserve samples according to regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the DBGLPC POC immediately.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager. Additionally, verify that the site notified the sponsor, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Collect and ship samples of the test and reference drug products **in their original containers** to this address:

Benjamin Westenberger, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101
TEL: (314) 539-2135

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

¹Retention of Bioavailability and Bioequivalence Testing Samples, Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993 located at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>

²CDER's Guidance for Industry, Handling and Retention of BA and BE Testing Samples, May 2004, located at <http://www.fda.gov/downloads/regulatoryinformation/guidances/UCM126836.pdf>

During the clinical site inspection, please:

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.
- Compare the study records in the NDA submission to the original documents at the site.
- Check for evidence of under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection:_____
 - o Number of subjects screened at the site:_____
 - o Number of subjects enrolled at the site:_____
 - o Number of subjects completing the study:_____
- Verify from source documents that case report forms accurately report evaluations related to the primary endpoint.
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

SECTION C - AUDIT OF ANALYTICAL DATA

Analytical Site:

(b) (4)

Investigators:

(b) (4) for study PA32540-115
(b) (4) for study PA8140-102

Methodology:

LC-MS/MS

During the analytical site inspection, please:

- Examine all pertinent items related to the analytical method used for the measurement of acetylsalicylic acid concentrations in human plasma.
- Compare the accuracy of the analytical data provided by the applicant in the NDA submission against the original documents at the site.
- Determine if the site employed a validated analytical method for the analysis of subject samples.
- Compare the assay parameters observed during the study sample analysis with those obtained during method validation. These parameters may include variability between and within runs, accuracy and precision, etc.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- Confirm that the site conducted an evaluation of analyte interference among acetylsalicylic acid, omeprazole, omeprazole sulfone, and 5-hydroxyomeprazole.
- Determine if site personnel analyzed subject samples within the validated stability period.
- Confirm that site personnel used freshly made calibrators and/or freshly made QCs for stability evaluations during method validation.
- Confirm that the precision and accuracy was demonstrated at least one time using QCs and calibrators prepared from separate stock solutions.

- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria such as the number of freeze-thaw cycles sufficiently covered the stability of reanalyzed subject samples.
- Examine the content of correspondence files between the analytical site and the sponsor.

Additional instructions to ORA Investigator:

The DBGLPC POC will provide you with compliance program elements, and in certain situations, additional study specific instructions prior to the inspections. Please contact the DBGLPC POC for inspection-related questions and clarifications before, during, and after the inspections.

If you issue a Form FDA 483, please remind the inspected site of the 15 business-day timeframe for submission of a written response to observations listed on the form. Promptly fax or email a copy of the form to the DBGLPC POC. If it appears that the site violations may warrant an OAI classification, notify the DBGLPC POC as soon as possible. Fax or email any written response to Form FDA 483 as soon as you receive it to Dr. Sam H. Haidar and the DBGLPC POC. Please address the EIR to Dr. Haidar:

Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
Office of Compliance
Bldg. 51 Rm. 5330
10903 New Hampshire Ave.
Silver Spring, MD 20993
Fax: 1-301-847-8748
Email: sam.haidar@fda.hhs.gov

DBGLPC POC: Ruben C. Ayala, Pharm.D.
Pharmacologist
Office of Scientific Investigations
Phone: 1-301-796-2018
Fax: 1-301-847-8748
Email: ruben.ayala@fda.hhs.gov

Page 7 - BIMO Assignment, NDA 205-103, aspirin/omeprazole tablets sponsored by POZEN, Inc.

CC:

CDER OSI PM TRACK

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CDER/OND/DGIEP/Griebel/Davis

CDER/OTS/OCP/Lee/Jappar

HFR-CE250/ [REDACTED] (b)(4) (BIMO)

HFR-SW150/ [REDACTED] (b)(4) (DIB)

HFR-SW1540 [REDACTED] (b)(4) (BIMO)

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Edit: MFS 6/21/13

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/s/

RUBEN C AYALA
10/24/2013

CHARLES R BONAPACE
10/24/2013



Center for Drug Evaluation and Research

Division of Cardiovascular and Renal Products

Consultation, NDA 205103

DATE: Consult requested: 30 April 2013
Consult request amended: June 07, 2013
Consult request amended: 18 September 2013
Desired completion date: 23 September 2013
Consult amended: 18 Oct 2013
Consult completed: 18 September 2013

FROM: Preston M. Dunnmon, M.D., Medical Officer
Division of Cardiovascular and Renal Products, HFD-110

Sudharshan Hariharan, Ph.D., Reviewer
Office of Clinical Pharmacology, DCP1

Rajanikanth Madabushi, Ph.D., Team Leader
Office of Clinical Pharmacology, DCP1

THROUGH: Norman Stockbridge, M.D., Ph.D., Division Director
Division of Cardiovascular and Renal Products, HFD-110

Stephen M. Grant, M.D., Deputy Director
Division of Cardiovascular and Renal Products, HFD-110

TO: CDR Anissa Davis, SRPM, DGIEP, 301-796-5016
CDR Stacy Barley, SRPM, DGIEP, 301-796-2137

SPONSOR: POZEN, Inc.
DRUG CLASS: Combination Proton Pump Inhibitor and Aspirin
DRUG NAME: PA8140 and PA32540 (enteric coated aspirin/immediate release omeprazole)

FORMULATION: PO
APPLICATION No: NDA 205103

PROPOSED INDICATION:

(b) (4)

DOCUMENTS AVAILABLE FOR REVIEW: NDA 205103

1. BACKGROUND

PA Tablets were developed as a PPI and aspirin containing tablet in a coordinated delivery system that is intended to provide the cardio-protective benefits of aspirin while reducing aspirin-related UGI damage and thus improving adherence.

This 505(b)2 application presents pharmacokinetic and pharmacodynamic data on PA Tablets to establish the bridge to the reference listed drugs (RLD) Ecotrin[®] (325 mg and 81 mg) and Prilosec[®].

Clinical safety and efficacy were assessed in 1429 subjects with a history of established cardiovascular disease receiving daily 325 mg aspirin and at risk of developing aspirin-associated gastric ulcers in the two controlled studies of 6-months duration (PA32540-301 and PA32540-302) as well as in a 12-month, open-label, safety study (PA32540-303).

Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Cardiovascular and Renal Products (DCaRP) about questions related to (i) review of major adverse cardiovascular events in patients receiving clopidogrel concomitantly from the efficacy trials, (ii) lack of bioequivalence of the aspirin components between PA32540 and Ecotrin[®] 325 mg, (iii) review of PLR labeling specific to the aspirin component, and (iv) drug interaction potential of the omeprazole component in PA32540 with clopidogrel. These consult questions are listed below in detail along with appropriate responses.

2. CONSULT QUESTIONS

Q.1 Applicant has provided an Integrated Summary of Safety of data from Studies 301 and 302 that includes an analysis of Cardiovascular Events of Special Interest (Section 2.4.2). MACE were observed in both studies and applicant also provides an analysis of MACE in patients who received clopidogrel concomitantly. Do the adjudicated and unadjudicated analyses presented by the sponsor, including the analysis of MACE in subjects who took clopidogrel, warrant inclusion in the label? Do these analyses suggest a new safety concern?

Critical to any assessment of cardiac safety is an understanding of the trial designs, populations assessed, pooling methods, population exposures, ascertainment methodologies for MACE events, data flow to the clinical events committee (CEC), MACE definitions, and MedDRA preferred term groupings (i.e., SMQs) that were used as automated system triggers for identifying potentially missed MACE outcome events

based on manual reporting. Understanding these elements, the actual MACE data can be reasonably interpreted. For this sponsor's development program, a summary of these important components are as follows.

Phase 3 Trials

PA32540-301: A 6-Month, Phase 3, Randomized, Double-Blind, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric-Coated Aspirin 325 mg in Subjects Who Are at Risk for Developing Aspirin-Associated Ulcers

- Males or non-pregnant, non-breastfeeding females who had been on daily (at least 5 days per week) aspirin 325 mg for at least 3 months and who were expected to use daily aspirin 325 mg for at least 6 months, and who were
 - 55 years of age and older; or
 - 18-54 years of age with a history of a documented gastric or duodenal ulcer within the past 5 years
- Aspirin was used for the secondary prevention of the following cardiovascular or cerebrovascular events:
 - Diagnosis or history of:
 - Confirmed or suspected myocardial infarction (MI);
 - Ischemic stroke; or
 - Transient ischemic attack (TIA).
 - Or established, clinically significant coronary and other atherosclerotic vascular disease (i.e., high risk for surgical intervention or for MI, TIA, stroke, if left untreated), including:
 - Angina (stable or unstable);
 - Peripheral arterial disease;
 - Atherosclerotic aortic disease; or
 - Carotid artery disease.
 - Or history of:
 - Coronary artery bypass graft (CABG);
 - Percutaneous coronary intervention (PCI) with or without stent; or
 - Carotid endarterectomy.

PA32540-302: A 6-Month, Phase 3, Randomized, Double-Blind, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric-Coated Aspirin 325 mg in Subjects Who Are at Risk for Developing Aspirin-Associated Ulcers

- Same eligibility criteria as study 301

PA32540-303: A 12-Month, Phase 3, Open-Label, Multi-Center Study to Evaluate the Long-Term Safety of PA32540 in Subjects Who Are at Risk for Developing Aspirin-Associated Gastric Ulcers

- Same eligibility criteria as studies 301 and 302

Population Definitions

Primary Safety Population (PSP) - all subjects randomized in the 6-month active-controlled studies PA32540-301 and PA32540-302. The adverse events seen in subjects who were treated with PA32540 are directly compared to those subjects who were treated with EC-aspirin 325 mg.

Long-term Safety Population (LSP) - all subjects who entered open-label study PA32540-303 and received at least one dose of PA32540 drug in study PA32540-303.

Twelve-Month Population (TMP) - subjects from open-label study PA32540-303 that completed at least 348 days of treatment with PA32540

Six-Month Population (SMP) - subjects from studies PA32540-301, PA32540-302 and PA32540-303 who were on treatment at least 168 days

Normal Healthy Volunteers (NHV) - subjects from the NHV studies were not pooled for safety analysis with patients from studies 301, 302, and 303 due to the variable designs of these studies (including cross-over designs).

Extent of exposure

Overall, 1221 subjects were exposed to PA32540 for up to 12 months. Of these, 321 subjects were healthy volunteers in eleven Phase 1 studies and 900 subjects were exposed in the three Phase 3 studies. Of the 900 Phase 3 subjects, 735 were exposed for 6 months and 290 for 12 months (Clinical Summary of Safety Section 2.7.4.1.2), a total of 548 patient years of exposure (ISS Table S1.3.1). Eighty-six subjects were exposed to PA8140. (Clinical overview page 22)

Table 2: Exposure by Population, PA Tablets and EC-aspirin

	Subjects	
	PA32540	EC-aspirin 325 mg
All Studies	1221	803
NHV	321	279
All Phase 3	900	524
Population		
Primary Safety Population (PSP)	521	524
Long-term Safety Population (LSP)	379	NA
Twelve Month Population (TMP)	290	NA
Six Month Population (SMP)	735	366
	Subjects	
	PA8140	EC-aspirin 81 mg
NHV	86	126

Note: NA = not applicable.

Source: Table S1.1, Table S1.2, Table S1.3, Table S2.1, and Table S3.1; Table 14.1.1, PA08140-101; Table 14.3.1, PA8140-102; Table 14.1.1, PA325-102; Table 14.1.1, PA32540-111; Table 14.1.1, PA32540-303.

MACE Ascertainment and Definitions

An independent Cardiovascular Review Committee (CRC), consisting of 3 Board Certified cardiologists who had staff level experience or privileges as a cardiologist at a medical institution performed a blinded review and adjudication of major adverse cardiovascular events (MACE). Briefly, the POZEN Medical Monitor (MM) reviewed all cardiovascular events identified by the sites and study monitors for CRC review. If the POZEN MM agreed the event may constitute a potential MACE, the event was reviewed by the CRC. If the POZEN MM did not agree, the CRC Chair reviewed the AE and if he determined the event constituted a potential MACE, the event was reviewed by the CRC. In addition, the POZEN MM periodically reviewed the clinical database and AE Listings and the CRC Chair reviewed the cardiovascular AEs and all SAEs for potential clinically significant cardiovascular events that might have not been identified by the sites. The CRC adjudicated events to a MACE category using the criteria listed below (from ISS Table 5, pg 44):

Table 5: Cardiovascular Events and Definitions

Cardiovascular Event	Definition¹
Cardiovascular Death	
Sudden cardiac death (SCD):	An unexpected death in a previously stable patient. Patients in this category should have had recent human contact before the event. This includes patients who after attempted resuscitation were comatose and then died. Patients who have been out of contact for a prolonged or unknown period of time should be classified as unknown.
Fatal myocardial infarction (MI):	Death from a cardiac event within 28 days of acute MI (including sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST elevation or new left bundle branch block (LBBB), and/or evidence of fresh thrombus by a coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood).
Pump failure death:	Death involving a substantive worsening of heart failure symptoms and/or signs resulting in augmentation or addition of heart failure therapies (O'Connor 2010).
Death due to stroke:	Death involving cerebral hemorrhage, cerebral infarct or cerebral embolism, in the absence of an MI.
Cardiac Procedure Death:	Death within 30 days of and related to a cardiac procedure.
Other Cardiovascular:	Death in which there is evidence of a primary cardiovascular etiology that cannot be classified as definite sudden death, MI, pump failure, stroke, or procedure-related (e.g., ruptured aortic aneurysm, aortic dissection, pulmonary embolism, cardiac tamponade).
Non-Fatal Events	
Non-Fatal MI	<p>Non-fatal MI was defined as presentation in a clinical setting consistent with myocardial ischemia with evidence of myocardial necrosis and alive 7 days after the index event. Non-fatal MI will also be characterized by Type as per UDMI criteria.</p> <p>Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:</p> <ul style="list-style-type: none"> • Symptoms of ischemia • Electrocardiogram (ECG) changes indicative of new ischemia (new ST-T changes or new LBBB) • Development of pathological Q waves in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Cardiovascular Event	Definition¹
Non-Fatal MI	<p>For percutaneous coronary interventions (PCI) in subjects with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.</p> <p>Stent thrombosis will be adjudicated according to Academic Research Consortium (ARC) criteria. Events judged as “definite” and “probable” stent thrombosis will meet this definition.</p> <p>For coronary artery bypass grafting (CABG) in subjects with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically-documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.</p> <p>Subjects presenting after randomization for routine evaluation or other reasons and who are found to have evidence of interval prior MI will be defined to have had non-fatal MI. Any one of the following criteria meets the diagnosis for prior MI:</p> <ul style="list-style-type: none"> • Development of new pathological Q waves with or without symptoms. • Imaging evidence of a region of loss of viable myocardium that is thinned • and fails to contract, in the absence of non-ischemic cause. • Pathological findings of a healed or healing MI.
Confirmed Ischemic Stroke	<p>Stroke is defined as a rapidly developing loss of brain function that is non-reversible and due to an interruption in the blood supply to all or part of the brain, and that persists for more than 24 hours, together with a diagnostic imaging study. PA32540 Phase 3 Program Page 9 of 10, Cardiovascular Review Committee Charter Version 1.0</p>
Unplanned Coronary Artery Bypass Graft Surgery	<p>Any Coronary Artery Bypass Graft Surgery that was unplanned prior to entry into the study</p>
Unplanned Percutaneous Coronary Intervention	<ul style="list-style-type: none"> • Any unplanned PCI, including any mechanical catheter-based revascularization techniques such as stenting, balloon angioplasty, coronary atherectomy or laser therapy. • Other surgical-based cardiac revascularization techniques (e.g., transmyocardial revascularization)

Cardiovascular Event	Definition ¹
Acute Coronary Syndromes (ACS)	Acute coronary syndromes are defined as a group of clinical syndromes compatible with acute myocardial ischemia, ranging from ST-segment elevation myocardial infarction (MI) to non-ST segment elevation MI and unstable angina. ACS without biological marker (unstable angina without detectable myocyte necrosis) is defined as non-ST-segment elevation ACS not accompanied by the release of markers of cell death (troponin and CK-MB), and is typically characterized by ECG changes of ST-segment depression or T-wave inversion or transient ST-elevation (Fox 2004a).
Other Adverse Cardiovascular Events	<ul style="list-style-type: none"> Heart failure or signs and symptoms of heart failure requiring hospital admission or emergency room visit and requiring intravenous therapy Transient ischemic attack less than 24 hours old, defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton 2009).
Non-Cardiovascular Deaths	<ul style="list-style-type: none"> Death due to causes such as infection, bleed, pulmonary, renal, cancer or other non-cardiovascular etiologies. Unknown death, defined as confirmed death, but without data to support mode of death. Death outside of the hospital without adequate source documentation or medical records will require a case narrative to be submitted by the investigator.

¹ Source: Appendix 9.5.1.1

MACE Data from Blinded Controlled Phase 3 Trials

The sponsor's analysis of treatment-emergent MACE (unadjudicated MACE) was based on a smaller set of preferred terms than used by the CEC for adjudicated MACE. Therefore, the listing of unadjudicated MACE events is smaller than was the case for adjudicated events. Importantly, the adjudicated MACE listing contained all of the unadjudicated MACE events. Summary results for both non-adjudicated and adjudicated MACE are shown below (from ISS table 59, pg 132, Primary Safety Population):

Table 59: Major Cardiovascular Events (MACE): Non-Adjudicated and Adjudicated Events

	Major Cardiovascular Events (MACE)					
	PA32540 N=521			EC-aspirin 325 mg N=524		
	Total Patient-Years =226.91			Total Patient-Years= 212.05		
	Event	Subject	Events Per 100 Patient Years Exposure	Event	Subject	Events Per 100 Patient Years Exposure
Non Adjudicated	6	5 (1.0%)	2.6	4	4 (0.8%)	1.9
Adjudicated	9	9 (1.7%)	4.0	14	13 (2.5%)	6.6

Source: S2.19.1, S1.3.1; and Table 14.3.2.2, PA32540-303; and ISS Appendix 9.5.1.4.

Noted is the fact that the adjudicated MACE rate for the PA32540 population was numerically lower when the CEC's more comprehensive dataset is used to count MACE events. The sponsor listed the breakdown of the MACE events, which for the non-adjudicated cases are as follows (from ISS table 54, pg 127, PSP, N=521 for PA32540, N= 524 for EC-aspirin 325mg):

Table 54: Subjects with Treatment Emergent Pre-Specified Major Cardiovascular Events (MACE) in the Primary Safety Population (PSP)

Study - Site / Subject	MACE	Adverse Event Preferred Term
PA32540		
302-499/3015	Non-Fatal Myocardial Infarction CV Death	Acute Myocardial Infarction Cerebrovascular Accident
302-572/4238	Non-Fatal Myocardial Infarction	Myocardial Infarction
302-676/4225	Non-Fatal Myocardial Infarction	Myocardial Infarction
302-860/4612	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction
302-862/4637	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction
EC-aspirin 325 mg		
301-455/2241	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction
301-509/1033	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction
302-664/4388	Non-Fatal Myocardial Infarction	Acute Myocardial Infarction

Source: Table S2.19.1 excluding one non-treatment emergent adverse event (subject 301-887/2639).

All of these cases captured by the sponsor were also identified by the CEC using the broader preferred term screen, as is see below (from ISS table 55, pg 128, PSP, N=521 for PA32540, N= 524 for EC-aspirin 325 mg):

Table 55: Adjudicated Major Cardiovascular Adverse Events (Expanded Terms) in Primary Safety Population (PSP)

Study - Site / Subject	MACE Category	Adverse Event Preferred Term
PA32540		
301-856/2645	CAD	Non-Cardiac Chest Pain
302-676/4225	Non fatal MI	Myocardial Infarction
302-572/4238	Non fatal MI	Myocardial Infarction
302-860/4612	Non fatal MI	Acute Myocardial Infarction
302-862/4637	Non fatal MI	Acute Myocardial Infarction
302-499/3015	Non fatal MI	Acute Myocardial Infarction
302-860/4515	Planned Coronary Artery Bypass Graft	Arteriosclerosis Coronary Artery
302-489/4466	TIA	Reversible Ischaemic Neurological Deficit
302-660/3027	Heart Failure	Cardiac Failure Congestive
EC-aspirin 325 mg		
301-455/2241	Non fatal MI	Acute Myocardial Infarction
301-509/1033	Non fatal MI	Acute Myocardial Infarction
302-664/4388	Non fatal MI	Acute Myocardial Infarction
301-776/2650	ACS	Coronary Artery Occlusion
301-776/2650	ACS	Angina Pectoris
302-379/4241	ACS	Angina Pectoris
301-647/2532	TIA	Transient Ischaemic Attack
301-792/2505	TIA	Transient Ischaemic Attack
301-887/2639	CV Death	Sudden Cardiac Death
302-655/4256	ACS	Coronary Artery Disease
302-700/4421	ACS	Angina Pectoris
302-787/4604	TIA	Transient Ischaemic Attack
302-379/4302	TIA	Reversible Ischaemic Neurological Deficit
302-849/4653	Heart Failure	Cardiac Failure Congestive

Source: Table S2.19.1; and Appendix 9.5.1.4.

Reviewer's comment: As expected AMI and ACS predominate, with few cerebral vascular and CHF events.

Of note, the most striking differential outcome between the PA32540 and EC-aspirin 325 groups were based on the use of clopidogrel co-therapy, as seen below (from ISS table 56, pg 129, PSP, N=521 for PA32540, N= 524 for EC-aspirin 325 mg):

Table 56: Proportion of Subjects with Pre-Specified Major Cardiovascular Adverse Events by Concomitant Use of Clopidogrel in the Primary Safety Population from Studies PA32540-301 and PA32540-302

	Clopidogrel Use = Yes ¹				Clopidogrel Use = No	
	PA32540 n(%) (N=117)		EC-Aspirin 325 mg n(%) (N=115)		PA32540 n(%) (N=404)	EC-Aspirin 325 mg n(%) (N=409)
	Any Time	Within 7 Days	Any Time	Within 7 Days		
Subjects with Any Major CV AE	4 (3.4)	4 (3.4)	0	0	1 (0.2)	4 (1.0)
Non-Fatal Stroke	0	0	0	0	0	0
Non-Fatal Myocardial Infarction	4 (3.4)	4 (3.4)	0	0	1 (0.2)	3 (0.7)
CV Death	0	0	0	0	1 (0.2)	1 (0.2)

¹'Any Time' columns include subjects on clopidogrel at any time during the treatment period. 'Within 7 Days' columns include only MACE Adverse Events that occurred following at least 7 consecutive days of clopidogrel use.

Source: Table S2.19

DCRP Conclusions for Question 1:

- The number of events is too small and the duration of exposure too short to draw reliable conclusions about cardiac safety. Rather than including Table 59 above that demonstrates these small numbers (with more unadjudicated MACE events and fewer adjudicated MACE events with this drug), we suggest including a statement that simply states that the number of adjudicated MACE events was similar between the groups, but number of events is too small and the duration of exposure too short to draw reliable conclusions about cardiac safety.
- Even in this small dataset, all MACE events in clopidogrel-treated patients occurred in the group receiving omeprazole (as PA32540). Given the well-known interaction between clopidogrel and omeprazole, the label for PA32540, if approved, should reflect the warning regarding clopidogrel and omeprazole as is currently included in the omeprazole label.

Q.2 According to sponsor's analysis, PA32540 (test product) was not bioequivalent to Ecotrin 325 mg (reference product) in terms of bioavailability parameters of acetylsalicylic acid in a BE study using reference-scaled average bioequivalence approach. The point estimate for exposure (AUC) to acetylsalicylic acid was 10-15% lower for PA32540 Tablets compared to Ecotrin 325 mg, however, the lower limit of the 90% confidence interval was outside the scaled BE range. The sponsor states that: "These results suggest that some subjects may absorb slightly less than the intended 325mg of aspirin. Because the relevant antithrombotic effects of aspirin have been demonstrated to occur over the dose range of 50-325mg, this observed small difference in acetylsalicylic acid exposure is not clinically meaningful." Does DCRP agree with sponsor's statement?

The only generally accepted and well-understood mechanism by which aspirin reduces the risk of adverse CV events is through inhibition of platelet aggregation via irreversible

acetylation of the cyclooxygenase-1 (COX-1) enzyme. Inhibition of COX-1 prevents conversion of arachidonic acid to thromboxane A2 (TxA2), which a potent agonist of platelet aggregation and therefore of thrombosis. Dose-response studies with aspirin have been conducted in past. A publication from Patrignani *et al*¹ shows that aspirin produces greater than 90% inhibition of serum thromboxane B2 (TxB2, the stable breakdown product of TxA2) following a single 100- mg dose. Upon repeat dosing at 0.45 mg/kg (equivalent to 31.5 mg for a 70 kg human), the authors report 95% inhibition of serum TxB2 by day 4. Similar results were also reported by Buerke and colleagues² where >95% inhibition of serum TxB2 was achieved by day 7 with 40 mg of loading and maintenance dose of aspirin which was no different when compared to aspirin treatment regimens with initial loading doses of 100, 300 or 500 mg and maintenance doses of 40 or 100 mg. The results provide evidence that upon repeat administration near maximal inhibition of serum TxB2 is attained at aspirin doses 81 mg or lower. Therefore, 10-15% lower exposure to aspirin for PA32540 tablets compared to Ecotrin[®] 325 mg is not clinically meaningful as this change in aspirin plasma exposures at 325 mg does not affect platelet inhibition.

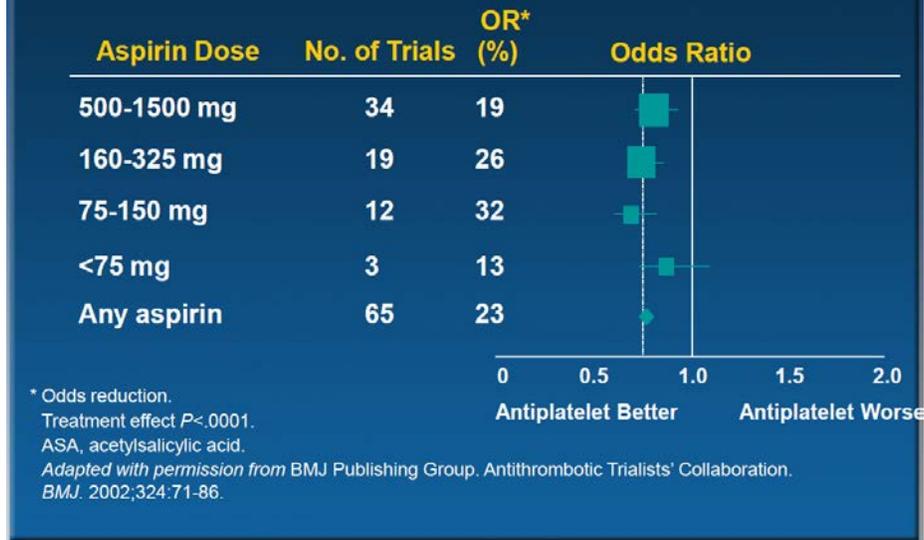
The discussion above begs the question whether anyone "needs" high dose maintenance aspirin, as was tested in this development program, for the secondary prophylaxis if CV events. The STEMI and NSTEMI guideline writing committees for the American College of Cardiology have recently re-evaluated the evidence for aspirin dosing in which the low dose of aspirin was given a Class IIa recommendation as opposed to higher doses of aspirin. Evidence to support this recommendation came first from the "Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death (CV or unknown cause), non-fatal myocardial infarction, and non-fatal stroke in high risk patients" (BMJ. 2002;324:71-86). This meta-analysis had the following important design elements and outcomes:

- Information about serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) was available from 195 trials of antiplatelet treatment versus control
- 7705 (10.7%) serious vascular events were recorded among 71,912 high risk patients allocated antiplatelet therapy versus an adjusted total of 9502 (13.2%) among 72,139 allocated control (P < 0.0001)
- The effects of different dose ranges of aspirin were assessed. At or above 75 mg per day, no particular range of aspirin dose was preferable for the prevention of serious vascular events. The proportional reduction in vascular events was:
 - 19% with 500-1500 mg daily
 - 26% with 160-325 mg daily
 - 32% with 75-150 mg daily,
 - 13% for daily doses <75 mg
- A figure of these results is shown below (slide from the ACCF 2013 Board Review, de Lemos):

¹ Patrignani P, Filabozzi P, Patrono C. *J Clin Invest.* 1982 Jun;69(6):1366-72.

² Buerke M, Pittroff W, Meyer J, Darius H. *Am Heart J.* 1995 Sep;130:465-72.

Indirect Comparisons of ASA Doses on Vascular Events in High-Risk Patients



Subsequently, the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) investigators evaluated the benefits and risks of adding clopidogrel to different doses of aspirin in the treatment of patients with acute coronary syndrome (ACS) (Circ. 2003; 108:1682-1687). The CURE trial and its aspirin-substudy assessing outcomes by aspirin dose had the following important design elements and outcomes:

- A double-blind, placebo-controlled trial of 12,562 patients with ACS receiving aspirin, 75 to 325 mg daily, randomized to clopidogrel or placebo for up to one year.
- The two primary outcomes of the CURE trial were
 - The composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke, and
 - The composite of the first primary outcome or refractory ischemia.
- The secondary outcomes were severe ischemia, heart failure, and the need for revascularization.
- Major bleeding was defined as being significantly disabling, intraocular bleeding leading to significant loss of vision, or bleeding requiring transfusion of 2 or 3 units of red blood cells or equivalent whole blood. Major bleeding was subclassified as life-threatening or other major bleeding. Life-threatening bleeding complications were defined as fatal or leading to a drop in hemoglobin of ≥ 5 g/dL or significant hypotension with the need for inotropes, requiring surgery (other than vascular site repair) or symptomatic intracranial hemorrhage, or requiring transfusion of 4 or more units of red blood cells or equivalent whole blood.

- In the CURE aspirin substudy analysis, patients were divided into the following 3 aspirin dose groups: ≤ 100 mg, 101 through 199 mg, and ≥ 200 mg.
- The combined incidence of cardiovascular death, myocardial infarction, or stroke was reduced by clopidogrel regardless of aspirin dose, as follows: ≤ 100 mg, 10.5% versus 8.6% (relative risk [RR], 0.81 [95% CI, 0.68 to 0.97]); 101 to 199 mg, 9.8% versus 9.5% (RR, 0.97 [95% CI 0.77 to 1.22]); and ≥ 200 mg, 13.6% versus 9.8% (RR, 0.71 [95% CI, 0.59 to 0.85]).
- GI bleeding increased significantly with increasing aspirin dose in both the placebo and the clopidogrel groups (from publication text – data not shown)
- The incidence of major bleeding increased with increasing aspirin dose both in the placebo group (1.9%, 2.8%, and 3.7%, respectively; $P=0.0001$) and the clopidogrel group (3.0%, 3.4%, and 4.9%, respectively; $P=0.0009$), as seen in the figure below:

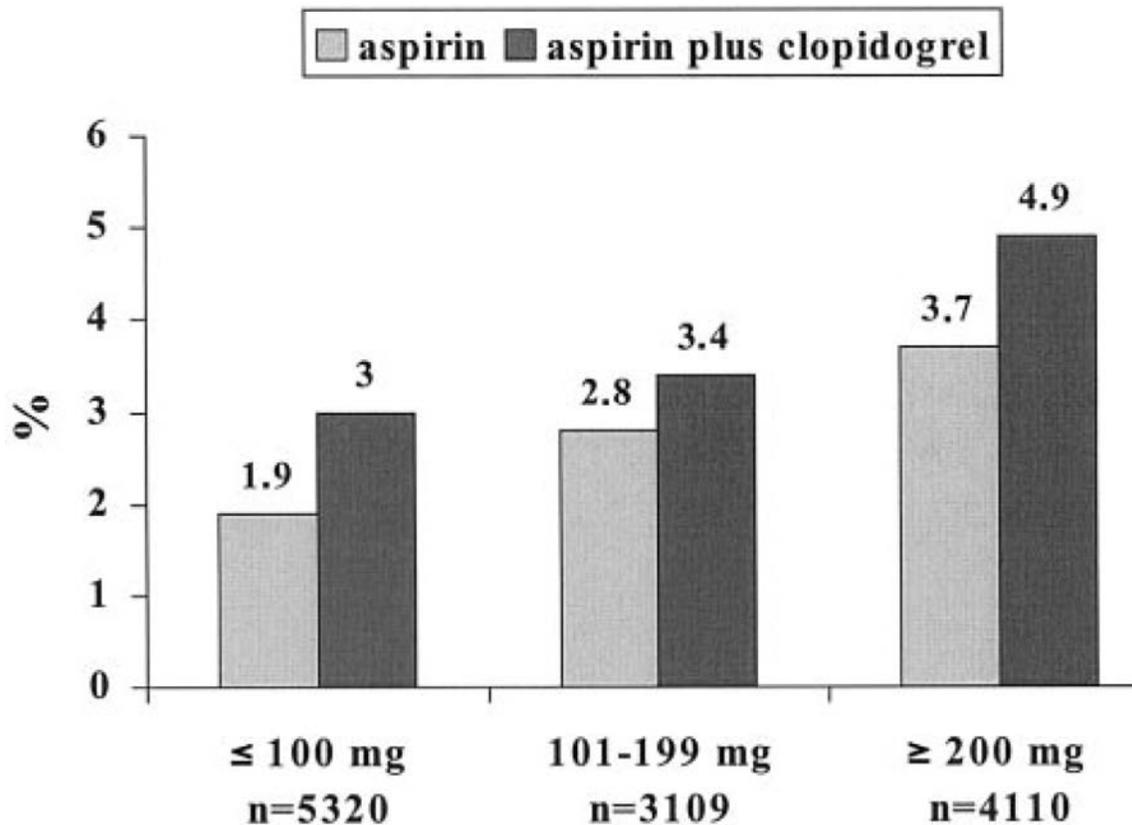


Figure 3. Aspirin dose and the incidence of major bleeding.

Further evidence suggesting an increase in major bleeding with increasing doses of aspirin without offsetting incremental efficacy in patients with CV disease and/or hypertension came from a large meta-analysis by Serebrauny et al (Am J Card 2005;95:1218). In this meta-analysis, major bleeding events were defined differently across the 31 studies (192,036 patients) that were eligible for analysis (mostly TIMI and

GUSTO definitions). The trials included in this meta-analysis are shown in the table below from that publication:

Trial (ref no.)	Total in the trial (n)	Patients on ASA (n)	Bleeding Events*					
			Total	Minor	GI	Major	Fatal/life Threat	Stroke
ASA <100 mg								
DUTCH TIA ⁸	3,131	1,555	89	49	14	40	11	13
ESPS-2 ⁹	6,602	1,649	135			20		
SAPAT ¹⁰	2,035	1,009	27	7	11	20		5
HOT ¹¹	1,879							
	0	9,399	292	156	102	129	7	14
Thrombosis prevention trial ¹²	5,499	1,268		484	5	8		2
SALT ¹³	1,360	676	49		9	20	10	
CURE ²	6,303	948	35	4	6	19	6	1
ACE ¹⁴	2,849	698			8	12	2	4
PPP ¹⁵	4,495	2,226	24		17			2
ASA 100–200 mg								
2nd SYMPHONY ¹⁶	6,671	2,231		234		89		1
SYMPHONY ¹⁷	9,172	3,074	570	386		120		1
STAMI ¹⁸	1,470	736				7		
	1,335							
PEP ¹⁹	9	6,679				13		
CARS ²⁰	8,803	3,281				57		
	2,110							
CAST ²¹	6	10,554				86	39	115
CHAMP ²²	5,059	2,357		77		50	7	15
CURE ²	6,303	3,311	152	43	13	77	29	1
ASA >200 mg								
DUTCH TIA ⁸	3,131	1,576	137	84	21	53	18	15
EAF ²³	1,007	404		29	10	6	6	2
AFASAK 2 ²⁴	677	169	31	26		5		1
MUST-I ²⁵	622	153						1
UK-TIA ²⁶	2,435	810			25			7
STARS ²⁷	1,965	557	10					
ACE ¹⁴	2,849	697			6	13	2	6
	1,943							
IST ²⁸	5	9,720						87
	8,767							
US NURSE ²⁹	8	87,678						62
	2,207							
PHSRG ³⁰	1	11,037				364		23
SPAF-II ³¹	1,100	545						6
	1,718							
ISIS-2 ³²	7	8,587						5
	1,918							
CAPRIE ³³	5	9,586	890		255	149		47
CREDO ³⁴	2,116	1,063		59		71		
WARSS ³⁵	2,206	1,103		259		30	5	
SPAF-III ³⁶	892	892				11		2
CURE ²	6,303	2,044	297	107	28	81	78	3
ACE ¹⁴	2,849	703			8	18	3	9
TASS ³⁷	3,069	1,540	152					
ACE ¹³	2,849	706			8	17	3	8
UK-TIA ²⁶	2,435	815			39			7

The meta-analysis demonstrated a dose-responsive relationship with aspirin and major bleeding that was statistically significant, as shown in the figure below from that publication:

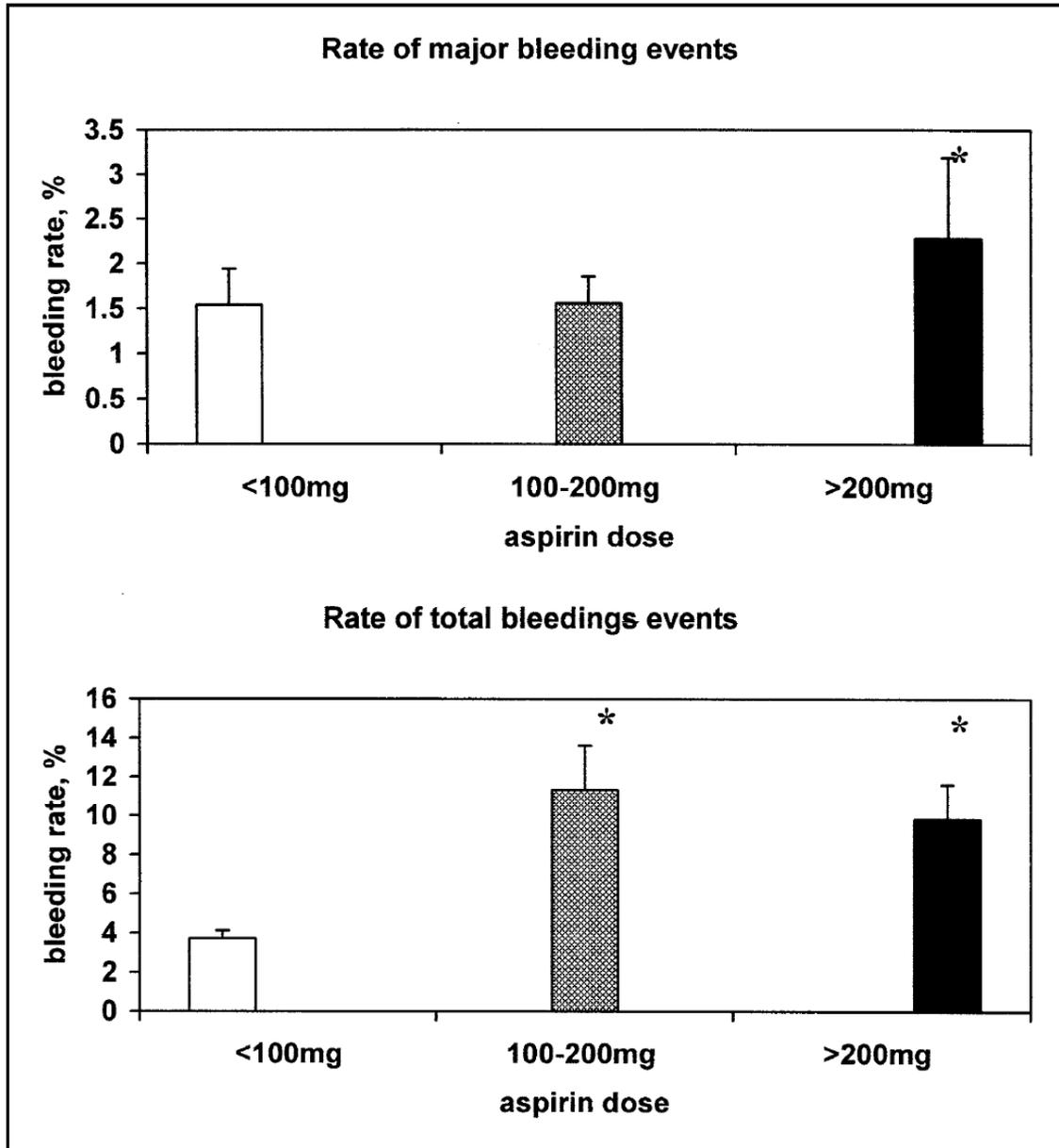
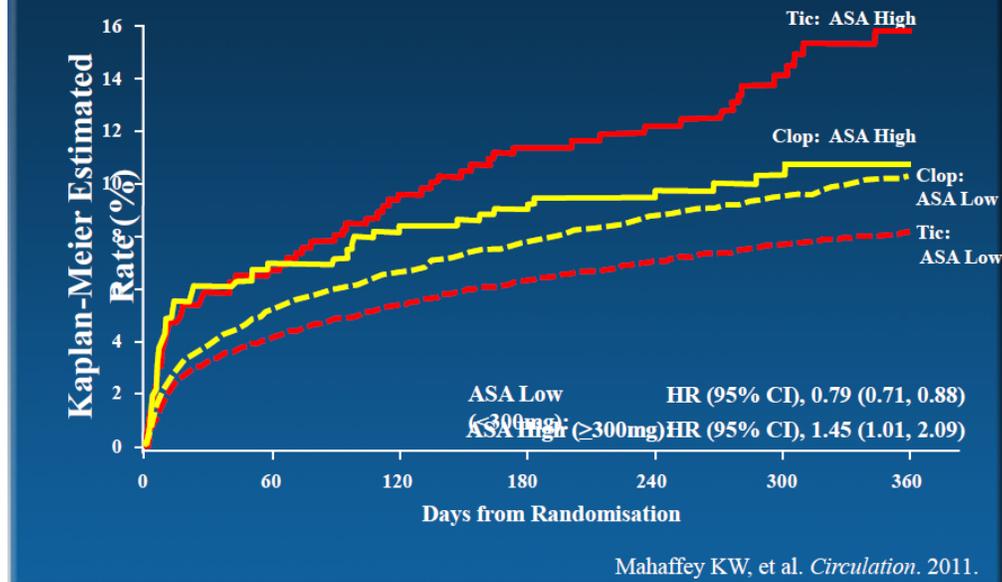


FIGURE 1. The rate of major and total bleeding complications. *p <.005.

More recently from PLATO, low dose aspirin cotherapy with ticagrelor was associated with fewer primary efficacy outcome events (CV death, MI or stroke) as compared to high dose aspirin cotherapy, as seen in the figure below:

PLATO: Primary Efficacy Outcome by ASA Maintenance Dose



Most importantly and most definitively, however, was the randomized, prospective comparison of high-dose versus low-dose aspirin that was performed in OASIS-7, a contemporary mega-trial of antiplatelet therapy in NSTEMI patients with the following design elements and outcomes:

- A 2-by-2 factorial, DB study of 25,000 patients with ACS with planned invasive strategy randomized to either high-dose clopidogrel (a 600-mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg daily thereafter) and a loading dose of 325 mg on day one and then either high-dose aspirin (300 to 325 mg daily) or low-dose aspirin (75 to 100 mg daily)
- Primary outcome of CV death, MI, or stroke at 30 days
- 99+% underwent coronary angiography (so clearly there was intent to revascularize the subjects mechanically but about a third did not get a PCI). Of the ~8000 subjects who did not undergo PCI, 45% had no clinically significant coronary artery disease, 24% underwent CABG, and 31% were not candidates for any type of revascularization.
- Efficacy outcomes were indistinguishable for the high vs. low aspirin doses: 4.2% vs. 4.4% for primary efficacy outcome (hazard ratio, 0.97; 95% CI, 0.86 to 1.09; P=0.61)
- A study-specific definition of major bleeding was used per table 3 below from the OASIS-7 publication, but TIMI criteria for major bleeding were also reported

- Major bleeding rates (study definition) for high and low aspirin doses were the same: 2.3% vs. 2.3% (hazard ratio, 0.99; 95% CI, 0.84 to 1.17; P=0.90), however there was more minor bleeding for the high versus the low aspirin doses: 5.0% vs. 4.4% (hazard ratio, 1.13; 95% CI, 1.00 to 1.27; P=0.04)
- The rate of GI bleeding was higher for the high vs. low aspirin doses: (47 patients [0.4%] vs. 29 patients [0.2%], P = 0.04).
- The important outcomes of this trial, by aspirin dose group, are shown in the table below (from the CURRENT–OASIS 7 Investigators. N Engl J Med 2010;363:930-942):

Table 3. Major Outcomes at 30 Days, According to Dose of Aspirin.*

Outcome	Higher Dose (N=12,507) number (percent)	Lower Dose (N=12,579) number (percent)	Hazard Ratio (95% CI)	P Value
Primary outcome: death from cardiovascular causes, myocardial infarction, or stroke	530 (4.2)	549 (4.4)	0.97 (0.86–1.09)	0.61
Secondary outcomes				
Death from cardiovascular causes, myocardial infarction, stroke, or recurrent ischemia	563 (4.5)	608 (4.8)	0.93 (0.83–1.04)	0.21
Death from cardiovascular causes	259 (2.1)	289 (2.3)	0.90 (0.76–1.06)	0.22
Myocardial infarction	253 (2.0)	261 (2.1)	0.97 (0.82–1.16)	0.76
Stroke	70 (0.6)	59 (0.5)	1.19 (0.84–1.68)	0.32
Recurrent ischemia	41 (0.3)	65 (0.5)	0.63 (0.43–0.94)	0.02
Death from any cause	273 (2.2)	314 (2.5)	0.87 (0.74–1.03)	0.10
Bleeding				
Major				
Study criteria	282 (2.3)	286 (2.3)	0.99 (0.84–1.17)	0.90
Requiring red-cell transfusion ≥2 units	239 (1.9)	238 (1.9)	1.01 (0.84–1.21)	0.93
CABG-related	111 (0.9)	126 (1.0)	0.88 (0.68–1.14)	0.34
Severe	216 (1.7)	215 (1.7)	1.01 (0.84–1.22)	0.93
Leading to decrease in hemoglobin level ≥5 g/dl	115 (0.9)	122 (1.0)	0.95 (0.73–1.22)	0.67
Symptomatic intracranial	6 (0.05)	4 (0.03)	1.51 (0.42–5.33)	0.53
Fatal	16 (0.1)	15 (0.1)	1.07 (0.53–2.17)	0.85
TIMI criteria	197 (1.6)	181 (1.4)	1.09 (0.89–1.34)	0.39
Minor	618 (5.0)	551 (4.4)	1.13 (1.00–1.27)	0.04

* The percentages are Kaplan–Meier estimates of the event rates at 30 days. CABG denotes coronary-artery bypass grafting, and TIMI Thrombolysis in Myocardial Infarction.

We think this is likely to be the best and last data we will get on this subject. If there is no clear advantage of high dose aspirin in the setting which most clearly requires effective platelet inhibition, then it is very unlikely there is an advantage in other settings. We do not make much of the similarity of the bleeding outcomes; we know that over a longer period time the bleeding outcomes for the two doses are different. Fuster in the accompanying editorial states:

“First, when the dosing regimens of aspirin were evaluated on a risk–benefit basis, the lower-dose regimen emerged the winner, with equivalent efficacy but lower rates of minor bleeding than the higher-dose regimen. The lower rate of minor bleeding may not impress clinical trialists, but it certainly has relevance for our patients and their clinicians. It is time for the proponents of higher-dose aspirin to concede defeat and modify clinical practice.”

In his editorial, Fuster also recommended that all ACS patients receive low dose aspirin (75 - 100 mg/day) from day 2 onward following ACS regardless of whether they were treated with PCI, CABG, or medical therapy.

DCRP Conclusions for Question 2:

- The 10-15% lower exposure to aspirin for PA32540 tablets compared to Ecotrin® 325 mg is not clinically meaningful as this change in aspirin plasma exposures at 325 mg does not affect platelet inhibition.
- While there appears to be no incremental benefit in chronic administration of doses of ASA above 100 mg, it is generally accepted that there is a dose-related increase in bleeding – particularly gastrointestinal bleeding (nominally significant increase in GI bleeding demonstrated in both CURE and OASIS-7)
- The data about the relationship between aspirin dose and bleeding are persuasive despite essentially all of it coming from subjects who have not been randomized to the dose of aspirin (OASIS-7 randomized the aspirin dose)
- Finally, it should be noted that the patients for whom Pozen’s ASA+omeprazole will be indicated is a subpopulation at higher risk for adverse gastrointestinal events than the population for whom ASA is indicated in the professional label, 21CFR 341.80. The draft label submitted by Pozen states its product is: “indicated for patients who require aspirin ... (b) (4) in patients at risk for developing aspirin-associated gastric ulcers.” Furthermore, not all patients on ASA for prevention of CV disease were eligible to enroll in the two pivotal trials but rather the eligibility criteria allowed enrollment only of a subpopulation at higher risk of gastric ulcers.
- Given the lack of a dose-related increase in efficacy and a dose-related increase in harm, it seems to us that patients at sufficient risk for gastric ulceration to require chronic administration of a PPI should not be administered 325 mg of aspirin.

Q.3 Please provide a review of the proposed PLR labeling specific to the ASA component. If possible, DGIEP requests a .pdf of the proposed labeling with proposed revisions made as tracked changes.

A tracked changes version of the label with edits from DCaRP will be sent to DGIEP. Based on our response to the question above, we will recommend that you approve only the dose of ASA + omeprazole containing 81 mg of ASA. Also, because the ASA in ASA+omeprazole is enteric coated, the label should state that ASA+omeprazole is not indicated for use on day 1 of an acute myocardial infarction or on the day of PCI in patients not chronically taking ASA.

Q.4 Review the two platelet aggregation studies, PA32540-110 and PA32540-111 and provide recommendations on whether or what information from these studies should be included in the label. Note that the proposed label contains reference to platelet aggregation studies in Section 7.14 and Section 12.2.

Studies PA32540-110 and PA32540-111 have been reviewed. Based on the results, it is not possible to rule out an interaction between the omeprazole component of PA32540 and clopidogrel 75 mg either administered concomitantly or when separated by 10 h. The individual study reviews are provided in the Appendix.

APPENDIX

STUDY NO: PA32540-110

TITLE

A randomized, open-label, crossover study to evaluate the inhibitory effect of clopidogrel plus EC aspirin (325 mg) and clopidogrel plus PA32540 on platelet aggregation in healthy volunteers

BACKGROUND

Clopidogrel is an inactive prodrug requiring metabolism by cytochrome P450 isozymes, importantly CYP2C19, to form its active metabolite. The active metabolite acts by irreversibly binding to the P₂Y₁₂ receptor of platelets thereby inhibiting platelet aggregation. Clopidogrel is often co-administered with proton pump inhibitors (PPIs). Some PPIs are inhibitors of CYP2C19. By inhibiting CYP2C19, PPIs may decrease the formation of the clopidogrel active metabolite, thereby attenuating the desired effect of inhibiting platelet aggregation.

In the current study, the applicant aims to evaluate the pharmacodynamic interaction potential of the omeprazole component of PA32540 when co-administered with clopidogrel, concomitantly and at least 10 h apart.

OBJECTIVES

Primary:

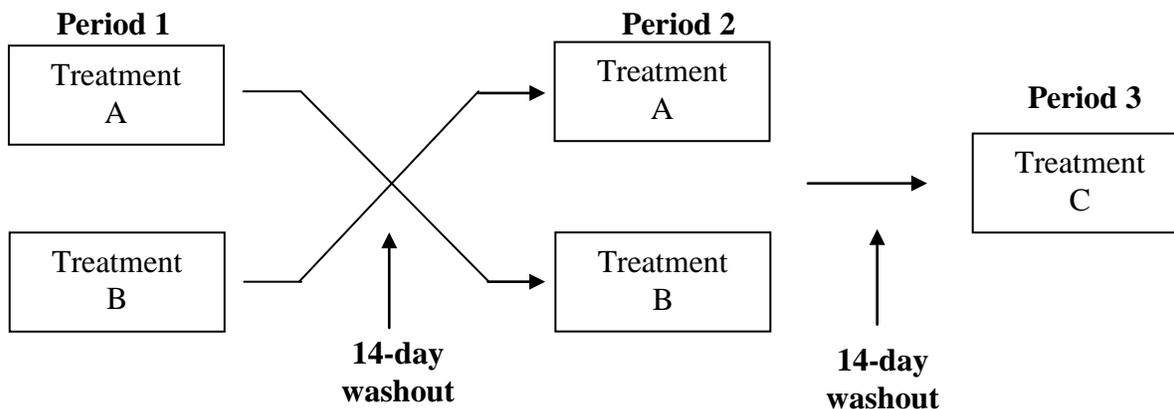
To compare inhibition of platelet aggregation induced by adenosine diphosphate (ADP) 20 µM between clopidogrel + EC aspirin 325 mg and clopidogrel + PA32540 treatment arms taken concomitantly and at least 10 h apart.

Secondary:

To compare inhibition of platelet aggregation between clopidogrel + EC aspirin 325 mg and clopidogrel + PA32540 treatment arms using – (i) ADP 5 µM, and (ii) arachidonic acid (AA) 2 mM as agonists; (iii) VerifyNow P₂Y₁₂ assay, (iv) VerifyNow aspirin assay, and (v) vasodilator stimulated phosphoprotein (VASP) phosphorylation assay.

STUDY DESIGN

A randomized, open-label, single-center, partial crossover study in healthy volunteers



Treatment arms:

A = Clopidogrel 300 mg + EC aspirin 325 mg on Day 1; clopidogrel 75 mg + EC aspirin 325 mg on Days 2-7

B = Clopidogrel 300 mg + PA32540 on Day 1; clopidogrel 75 mg + PA32540 on Days 2-7

C = PA32540 (morning) + clopidogrel 300 mg (afternoon) on Day 1; PA32540 (morning) + clopidogrel 75 mg (afternoon) on Days 2-7

Test products:

- EC aspirin = Ecotrin[®]
- Clopidogrel = Plavix[®]
- PA32540 = FDC of EC aspirin 325 mg with an outer coating of immediate release omeprazole 40 mg

Approximately 30 healthy adults were planned, enrolled, randomized and treated for the first two treatment periods and 28 of the same subjects were treated for the added third treatment arm.

Subjects were healthy adult males or non-lactating, non-pregnant females at least 40 years of age with a body mass index of 19 to 30 kg/m². Subjects were required to have \geq 70% platelet aggregation function at screening and could not have taken any antiplatelet drug or more than two 325 mg doses of aspirin (or other NSAID) within 2 weeks of the screening visit.

Reviewer's comment: Omeprazole is a mechanism based inhibitor of CYP2C19.

Therefore, maximal inhibition effects following the first dose of clopidogrel can only be observed upon pre-treatment with omeprazole which is not how the current study was designed.

PHARMACOKINETICS

No pharmacokinetic evaluation was performed.

Reviewer's comment: *Drug interactions between clopidogrel and PPIs have been primarily addressed by pharmacokinetic results i.e., exposure to the active metabolite of clopidogrel, with platelet inhibition data as supportive evidence.*

PHARMACODYNAMICS

Blood samples were obtained for platelet aggregation evaluation during the screening phase, prior to dosing on Day 1, approximately 24 h after Day 1 dosing and just prior to dosing on Day 2, and one hour after dosing on Day 7 of each period.

Platelet aggregation (PA) in response to clopidogrel and aspirin was primarily assessed by light transmittance aggregometry using ADP and AA, respectively as agonists. In addition, platelet function was also evaluated by VASP phosphorylation assay (receptor reactivity ratio, RRR), VerifyNow P₂Y₁₂ (P₂Y₁₂ reactivity unit, PRU) and VerifyNow aspirin (aspirin reactivity unit, ARU) assay.

Inhibition of platelet aggregation (IPA), % is calculated as in Eqn. (1). Inhibition of platelet function by other methodologies is also calculated similarly, but, substituting RRR, PRU and ARU, respectively for PA.

$$\text{IPA, \%} = [\text{PA}_{\text{bsln}} - \text{PA}_{\text{end}}] / \text{PA}_{\text{bsln}} * 100 \text{ ----- Eqn. (1)}$$

CYP2C19 GENOTYPING

No genotyping to determine CYP2C19 loss-of-function allele carrier status was performed.

SAMPLE SIZE DETERMINATION

The sample size was derived using a 2.5% one-sided test with 90% power to reject the null hypothesis that PA32540 + clopidogrel is inferior to EC aspirin 325 mg + clopidogrel at a non-inferiority margin of 10 units. The sample size and power calculations were made under the assumption that non-inferiority was to be tested with the expectation that the difference between PA32540 + clopidogrel and EC aspirin 325 mg + clopidogrel would be zero, that EC aspirin 325 mg + clopidogrel would have a mean IPA of 40 with a standard deviation of 12. The sponsor claims that the sample size also provided sufficient power to test the non-inferiority between sequentially administered PA32540 + clopidogrel (10 h apart) and EC aspirin 325 mg + clopidogrel.

Reviewer's comment: *A non-inferiority margin of 10% in platelet inhibition is not interpretable in terms of how it translates to clinical outcomes.*

STATISTICAL ANALYSIS

A mixed-effect ANOVA model on the pharmacodynamic parameter (e.g., IPA %) was fitted with sequence, period and treatment as fixed effects and subjects within sequence as random effect. Two-sided 95% CI for the least square mean difference of the pharmacodynamic metric between PA32540 + clopidogrel and EC aspirin 325 mg + clopidogrel was calculated. In addition, paired mean differences and 95% CI were calculated between EC aspirin 325 mg + clopidogrel and sequentially administered PA32540 + clopidogrel (10 h apart). Non-inferiority was established if the upper bound of a two-sided 95% CI for LS mean difference between the two treatment arms in comparison was less than or equal to 10%.

RESULTS

Study subjects and disposition:

- All 30 randomized subjects completed the two treatment periods and therefore were included in the intent to treat (ITT) and safety populations. A total of 28 subjects completed the third sequential treatment period. Two subjects (7%) were prematurely withdrawn due to personal reasons.

Pharmacodynamics:

- Concomitant administration of PA32540 with clopidogrel 75 mg reduced the mean IPA by 15.1% and 16.6% relative to control on Day 7 with ADP 5 μ M and 20 μ M, respectively as agonist (Table 1). When PA32540 and clopidogrel 75 mg were administered 10 h apart, the mean IPA was reduced by 9.7% and 13.8% on Day 7 with ADP 5 μ M and 20 μ M, respectively as agonist (Table 1).
- Other platelet function assays also showed significant inhibition of platelet function when PA32540 was administered with clopidogrel 75 mg concomitantly or 10 h apart relative to EC aspirin 325 mg + clopidogrel on Day 7 (Table 2).
- The antiplatelet response measured after stimulation by AA is similar across both treatment arms.

Reviewer's comments:

- *Platelet aggregation results following Day 1 is not discussed further in this review as it may represent incomplete CYP2C19 inhibition. It is well known that omeprazole is a mechanism based inhibitor of CYP2C19 requiring pre-treatment to generate metabolites which inhibits the enzyme in an irreversible fashion. Therefore, maximal inhibition effects following the first dose of clopidogrel can only be observed upon pre-treatment with omeprazole which is not how the current study was designed. Studies performed earlier (NDA 20839; DARRTS date: 11/02/2009) where delayed release omeprazole 80 mg was administered for 5 days prior to administration of the loading dose of clopidogrel*

showed a 45% decrease in the plasma exposure to clopidogrel active metabolite with corresponding decreases in IPA.

- As mentioned earlier, relationship between platelet inhibition and clinical outcomes are poorly understood. A non-inferiority margin of 10% in platelet inhibition is non-interpretable in terms of how it translates to clinical outcomes. Due to this reason, the Division of Cardio-Renal Products has always used 80-125% bioequivalence limits to the plasma exposure of clopidogrel active metabolite as the primary basis to address drug interactions between clopidogrel and PPIs.

Safety:

- There were no deaths or other serious adverse events in the study and no withdrawals due to adverse events.

Table 1: Analysis of inhibition of platelet aggregation between treatment groups on Day 7 using ADP and AA as agonist

CROSSOVER PERIOD				
Assay	LS Mean (SE)		LS Mean Difference (95% CI)	% decrease relative to control
	A (N=30)	B (N=30)	A vs B	
ADP 20 µM	43.96 (2.31)	36.65 (2.31)	7.30 (1.44, 13.2)	16.6
ADP 5 µM	53.98 (2.49)	45.85 (2.49)	8.13 (2.53, 13.7)	15.1
AA 2 mM	91.15 (3.16)	91.41 (3.16)	-0.26 (-0.93, 0.41)	--
FIXED PERIOD				
Assay	Mean (SD)		Mean Difference (95% CI)	% decrease relative to control
	A (N=28)	C (N=28)	A vs C	
ADP 20 µM	44.39 (13.7)	39.97 (11.9)	4.41 (-0.78, 9.61)	9.96
ADP 5 µM	54.09 (15.1)	46.61 (14.1)	7.48 (0.89, 14.1)	13.8

Table 2: Analysis of inhibition of platelet function between treatment groups on Day 7 using RRR, PRU and ARU as agonist

CROSSOVER PERIOD				
Assay	LS Mean (SE)		LS Mean Difference (95% CI)	% decrease relative to control
	A (N=30)	B (N=30)	A vs B	
RRR	52.77 (3.61)	34.45 (3.61)	18.32 (10.7, 25.9)	34.7
PRU	56.12 (2.96)	32.75 (2.96)	23.37 (17.9, 28.8)	41.6
ARU	34.50 (1.73)	36.43 (1.73)	-1.93 (-5.97, 2.11)	--

FIXED PERIOD				
Assay	Mean (SD)		Mean Difference (95% CI)	% decrease relative to control
	A (N=28)	C (N=28)	A vs C	
RRR	51.85 (18.43)	41.73 (20.02)	10.12 (3.56, 16.7)	19.5
PRU	56.46 (16.92)	40.61 (18.8)	15.85 (9.87, 21.8)	28.1

CONCLUSION

Pharmacokinetics of the clopidogrel active metabolite was not characterized in this study. There is a decrease in platelet inhibition when clopidogrel is administered concomitantly with PA32540 relative to clopidogrel + EC aspirin 325 mg. Separation in the administration of PA32540 and clopidogrel by 10 h shows a relative increase in platelet inhibition compared to concomitant administration following the use of ADP 20 µM as agonist, however, with no internal consistency with results using ADP 5 µM. From an earlier study (NDA 20839, DARRTS date: 11/02/2009) we know that the platelet inhibition results are no different when clopidogrel is administered with delayed release omeprazole 80 mg concomitantly or separated by 12 h, due to the mechanistic irreversible inhibition of CYP2C19 by omeprazole. From another study (IND (b) (4) DARRTS date: 08/20/2012) which evaluated concomitant administration of clopidogrel 75 mg with delayed release omeprazole 20 mg, the mean AUC_{0-t} of clopidogrel active metabolite was decreased by 18% with the 90% CIs of the geometric mean ratio not contained within the bioequivalence limits of 80-125%. In the light of these findings and the absence of pharmacokinetic data, we recommend avoid use of PA32540 with clopidogrel when administered concomitantly or 10 h apart.

STUDY NO: PA32540-111

TITLE

A randomized, open-label, crossover study to evaluate the inhibitory effect of clopidogrel, EC aspirin 81 mg and EC omeprazole 40 mg all dosed concomitantly and PA32540 and clopidogrel dosed separately on platelet aggregation in healthy volunteers

BACKGROUND

Study PA32540-110 evaluated the pharmacodynamic interaction between EC aspirin 325 mg + clopidogrel and PA32540 + clopidogrel when dosed concomitantly and 10 h apart. The current study was conducted to provide further *ex vivo* data on the platelet inhibitory effect of PA32540 + clopidogrel when dosed separately (10 h apart) as compared to concomitant administration of EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel.

OBJECTIVES

Primary:

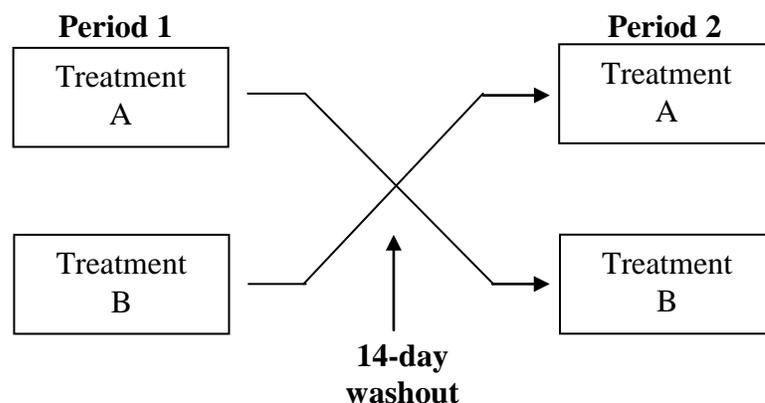
To evaluate ADP-induced platelet aggregation following administration of clopidogrel, EC aspirin 81 mg and EC omeprazole 40 mg all dosed concomitantly *vs* PA32540 and clopidogrel dosed separately.

Secondary:

To evaluate AA-induced platelet aggregation following administration of clopidogrel, EC aspirin 81 mg and EC omeprazole 40 mg all dosed concomitantly *vs* PA32540 and clopidogrel dosed separately.

STUDY DESIGN

A randomized, open-label, single-center, two-way crossover study in healthy volunteers



Treatment arms:

A = PA32540 (morning) + clopidogrel 300 mg (afternoon) on Day 1; PA32540 (morning) + clopidogrel 75 mg (afternoon) on Days 2-7

B = EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel 300 mg on Day 1; EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel 75 mg on Days 2-7

Test products:

- EC aspirin = Bayer[®]
- Clopidogrel = Plavix[®]
- EC omeprazole = Prilosec[®]
- PA32540 = FDC of EC aspirin 325 mg with an outer coating of immediate release omeprazole 40 mg

Approximately 30 healthy adult volunteers were planned, enrolled and randomized to the two treatment groups. Twenty nine subjects completed treatment A and 30 subjects completed treatment B.

Subjects were healthy adult males or non-lactating, non-pregnant females at least 40 years of age with a body mass index of 19 to 30 kg/m². Subjects were required to have ≥ 70% platelet aggregation function at screening and could not have taken any antiplatelet drug or more than two 325 mg doses of aspirin (or other NSAID) within 2 weeks of the screening visit.

PHARMACOKINETICS

No pharmacokinetic evaluation was performed.

Reviewer's comment: *Drug interactions between clopidogrel and PPIs have been primarily addressed by pharmacokinetic results i.e., exposure to the active metabolite of clopidogrel, with platelet inhibition data as supportive evidence.*

PHARMACODYNAMICS

Blood samples were obtained for platelet aggregation evaluation during the screening phase and prior to dosing on Day 1. On Day 7, subjects receiving treatment A had one blood sample drawn for AA-induced platelet aggregation evaluation 2 h after morning dosing of PA32540 and 2 additional blood samples taken for ADP-induced platelet aggregation evaluation 2 h after the evening dose of clopidogrel. Subjects receiving treatment B had blood samples drawn 2 h after their concomitant morning dose, one sample for AA-induced and 2 samples for ADP-induced platelet aggregation evaluation.

Platelet aggregation (PA) in response to clopidogrel and aspirin was primarily assessed by light transmittance aggregometry. Inhibition of platelet aggregation (IPA), % is calculated as in Eqn. (1).

$$\text{IPA, \%} = [\text{PA}_{\text{bsln}} - \text{PA}_{\text{end}}] / \text{PA}_{\text{bsln}} * 100 \text{ ----- Eqn. (1)}$$

CYP2C19 GENOTYPING

No genotyping to determine CYP2C19 loss-of-function allele carrier status was performed.

SAMPLE SIZE DETERMINATION

The sample size was derived using a 5% two-sided test with 90% power to detect a mean difference of 10% in IPA between PA32540 + clopidogrel dosed separately and EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel dosed concomitantly assuming that the mean IPA of PA32540 + clopidogrel dosed separately is 40 and the standard deviation of treatment differences is 14.

STATISTICAL ANALYSIS

A mixed-effect ANCOVA model on IPA % was fitted with sequence, period and treatment as fixed effects and subjects within sequence as random effect and baseline platelet aggregation as a covariate. Two-sided 95% CI for the least square mean difference between the treatment arms was calculated.

RESULTS

Study subjects and disposition:

- Thirty subjects completed treatment A and 29 subjects completed treatment B. One subject (3%) discontinued early due to an adverse event.

Pharmacodynamics:

- There was an 18.5% increase in mean IPA-induced by ADP 20 μ M when PA32540 + clopidogrel was administered 10 h apart when compared to EC aspirin 81 mg + EC omeprazole 40 mg + clopidogrel administered concomitantly. No significant differences in mean IPA-induced by AA 2 mM were found between the treatment arms.

Reviewer's comments:

- *Though there was a modest increase in mean IPA-induced by ADP 20 μ M with administration of PA32540 + clopidogrel 10 h apart, we do not know the platelet inhibitory effect relative to clopidogrel administered alone. In other words, this study lacks an appropriate control arm.*
- *As mentioned earlier, relationship between platelet inhibition and clinical outcomes are poorly understood. The Division of Cardio-Renal Products has always used 80-125% bioequivalence limits to the plasma exposure of clopidogrel active metabolite as the primary basis to address drug interactions between clopidogrel and PPIs.*

Safety:

There were no deaths or other serious adverse events in the study and no withdrawals due to adverse events.

Table 2: Analysis of inhibition of platelet aggregation between treatment groups on Day 7

Assay	LS Mean (SE)		LS Mean Difference (95% CI)	% increase relative to control
	A (N=30)	B (N=30)	A vs B	
ADP 20 μ M	46.50 (3.55)	39.25 (3.53)	7.24 (2.57, 11.9)	18.5
AA 2 mM	91.86 (1.27)	92.06 (1.25)	-0.21 (-3.61, 3.19)	--

CONCLUSION

This study lacks an appropriate control arm. The comparison of importance is the platelet inhibitory effects of PA32540 + clopidogrel administered 10 h apart relative to EC aspirin + clopidogrel. Based on the results from the previous study PA32540-110, we know that there is a decrease in mean IPA by approximately 10-14% when PA32540 is administered with clopidogrel separated by 10 h relative to clopidogrel + EC aspirin 325 mg. As the relationship between platelet inhibition and clinical outcomes is poorly understood, this interaction cannot be addressed in the absence of pharmacokinetic data.

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/s/

PRESTON M DUNNMON
10/21/2013

NORMAN L STOCKBRIDGE
10/21/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 205103

Application Type: Non-NME New NDA

Name of Drug: (b)(4) (aspirin/omeprazole) tablets, 81 mg and 325 mg aspirin/40 mg omeprazole

Applicant: POZEN, Inc.

Submission Date: March 25, 2013

Receipt Date: March 25, 2013

1.0 Regulatory History and Applicant's Main Proposals

POZEN submitted a new drug application which provides for a new formulation, aspirin and omeprazole, with the following proposed indication: secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers.

POZEN conducted a development program for PA8140 (aspirin 81 mg/omeprazole 40 mg tablets) and PA32540 (aspirin 325 mg/omeprazole 40 mg tablets) (aspirin/omeprazole) tablets (PA Tablets). The coordinated delivery formulation of PA tablets allows omeprazole to be immediately released while release of aspirin from the core is delayed dependent on pH. The Sponsor developed PA tablets to ensure that subjects who require chronic aspirin therapy will always receive a preceding PPI dose.

POZEN utilized literature as well as clinical studies to support this 505(b)(2) application. The reference listed drugs (RLD) for this application are Ecotrin® GSK (aspirin) and Prilosec® AstraZeneca (omeprazole).

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 60-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 7, 2013. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information (SRPI)

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *The HL covers approximately three-fourths of the page; however, a general waiver was granted on October 5, 2012 for Proton Pump Inhibitor labels to exceed the "less than or equal to one-half page". This product will be granted a waiver as well.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment: However, the word "BRANDNAME" was utilized instead of "TRADENAME" as a place holder until a proprietary name is approved; the dosage form was used along with the "BRANDNAME"; and the statement is italicized.

Product Title

- YES** 10. Product title in HL must be **bolded**.

Selected Requirements of Prescribing Information (SRPI)

Comment: However, the drug name must be followed by drug's dosage form (unless the dosage form is part of the drug name) and route of administration (ROA). For example "MYDRUG (drugozide) tablets, for oral use."

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

- N/A** 14. Must always have the verbatim statement "*See full prescribing information for complete boxed warning.*" centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement "*See full prescribing information for complete boxed warning.*")

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Selected Requirements of Prescribing Information (SRPI)

Comment:

Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment: *Pharmacologic class not annotated in statement.*

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment: *There is only one dosage form for this drug.*

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *However, the Sponsor's phone number is incomplete.*

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: *However, "and Medication Guide" is italicized.*

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

Selected Requirements of Prescribing Information (SRPI)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.
Comment:
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment: However, the word "experience" for the subsection "6.2 Post-marketing experience", the word "use" in sections 5.13 and 5.15, and the word "marketing" in section 6.2 should be capitalized..
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“*Sections or subsections omitted from the Full Prescribing Information are not listed.”**
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION

Selected Requirements of Prescribing Information (SRPI)

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *However, labeling is misspelled in the statement utilized.*

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

/s/

ANISSA A DAVIS
05/24/2013

BRIAN K STRONGIN
05/24/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205103 BLA# N/A	NDA Supplement #: S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: (b) (4) Established/Proper Name: aspirin/omeprazole Dosage Form: tablets Strengths: 81 mg and 325 mg aspirin/ 40 mg omeprazole		
Applicant: POZEN, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: March 25, 2013 Date of Receipt: March 25, 2013 Date clock started after UN: N/A		
PDUFA Goal Date: January 24, 2014		Action Goal Date (if different): N/A
Filing Date: May 24, 2013		Date of Filing Meeting: May 8, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 4		
Proposed indication(s)/Proposed change(s): secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 078747 and IND 70,477				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid (3/11/13) <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			Dated 1/31/13
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			PeRC meeting scheduled for September 25, 2013
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			Consult submitted to OPDP on 4/24/13
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Consult submitted to Patient Labeling on 4/24/13
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Consult submitted to OSE on 4/24/13
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined?			X	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			Consult to Division of Cardiovascular and Renal products submitted on 4/30/13
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 21, 2012; April 26, 2012 <i>If yes, distribute minutes before filing meeting</i>	X			Meetings 9/21/12 (Type A Meeting- to discuss bioequivalence and bridging) and 4/26/12 (Pre-NDA Meeting) under IND 078747
Any Special Protocol Assessments (SPAs)? Date(s): SPA-1, September 29, 2009 (Stability); SPA-2, July 29, 2008 (Clinical) <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			“No Agreement” for both SPA request

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 8, 2013

BLA/NDA/Supp #: NDA 205103

PROPRIETARY NAME: (b) (4) (1st choice); (b) (4) (2nd choice)

ESTABLISHED/PROPER NAME: (aspirin/omeprazole)

DOSAGE FORM/STRENGTH: Tablets; 81 mg and 325 mg aspirin/ 40 omeprazole

APPLICANT: POZEN, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers

BACKGROUND: POZEN conducted a development program for PA8140 (aspirin 81 mg/omeprazole 40 mg tablets) and PA32540 (aspirin 325 mg/omeprazole 40 mg tablets) (aspirin/omeprazole) tablets (PA Tablets). The coordinated delivery formulation of PA tablets allows omeprazole to be immediately released while release of aspirin from the core is delayed dependent on pH. The Sponsor 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.

POZEN utilized literature as well as clinical studies to support this 505(b)(2) application. The reference listed drugs (RLD) for this application are Ecotrin[®] GSK (aspirin) and Prilosec[®] AstraZeneca (omeprazole).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Anissa Davis (filing) Stacy Barley (post filing)	Y
	CPMS/TL:	Brian Strongin	N
Cross-Discipline Team Leader (CDTL)	Robert Fiorentino		Y
Clinical	Reviewer:	Zana Marks	Y
	TL:	Robert Fiorentino	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	

	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Dilara Jappar	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Milton Fan	Y
	TL:	Freda Cooner	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tamal Chakraborti	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Zhengfang Ge	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	N
	TL:	N/A	N
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	Y
	TL:	Lubna Merchant	Y

OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Khairy Malek	
	TL:	Susan Leibenhaut	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers: Biopharmaceutics and Quality Microbiology (non-sterile product)	Biopharmaceutics Reviewer: Banu Zolnik		Y
	Biopharmaceutics TL: Sandra Suarez Sharp		Y
	Quality Microbiology Reviewer: Jessica Cole		N
	Quality Microbiology TL: Bryan Riley		N
Other attendees	Pete Do (OSE RPM) Maria Walsh, Giuseppe Randazzo Vicki Moyer, Jeanine Best, Donna Synder, Joyce Korvick, Sandra Suarez, Courtney Suggs		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments: None</p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) 	<input type="checkbox"/> YES

needed?	<input type="checkbox"/> NO
BIOSTATISTICS Comments: None	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: None	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: no comments Microbiology Comments You propose to waive microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points: 1) Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. <ul style="list-style-type: none"> Address how the [REDACTED] (b) (4) are controlled for microbial growth [REDACTED] (b) (4) 2) Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188. 3) Describe activities taken when microbiological	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

acceptance criteria are not met at control points.

4) Provide an updated stability schedule to reflect the microbial limits testing (b) (4)

Biopharmaceuticals Comments

- 1) Provide solubility data for the drug substance covering the physiological pH range.
- 2) Provide data supporting the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent
- 3) Provide comparative dissolution profile of the batch 3078656R to the other clinical batches.
- 4) You have not provided In Vitro Alcohol Induced Dose Dumping Studies for both strengths as per recommended during IND 78,747 Type A Meeting minutes dated 9/21/2012. We are concerned that your delayed release (DR) product may release its entire contents (“dose dumping”) in the stomach when co-administered with alcohol defeating the purpose of the formulation. Therefore evaluate the potential for a drug-alcohol interaction with your DR product in in vitro settings.
 - Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed in 0.1 N HCl and in the proposed QC medium. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
 - The following alcohol concentrations for the in vitro dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
 - The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first

<p>2 hours.</p> <ul style="list-style-type: none"> The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference). 	
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: They were consulted to attend meetings as a new requirement for NDA submissions.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: Four of the five manufacturing sites, (b) (4) have been deemed acceptable; however, (b) (4) site is still pending</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: To be determined</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p>	

GOAL DATES	
Primary Reviews Due	December 20, 2013
Secondary Reviews Due	December 26, 2013
Labeling/REMS/PMR-PMC Comments to Sponsor	December 26, 2013
CDTL Review Due	January 3, 2014
PDUFA Date (January 25th is a Saturday)	January 24, 2014
Milestone Meetings	
Filing Meeting	May 8, 2013
Planning Meeting	June 3, 2013
Mid-Cycle Meeting	September 23, 2013
PeRC	September 25, 2013
<i>PeRC Paperwork Due: September 16, 2013</i>	
Wrap-up Meeting	December 16, 2013
Team Meetings	
1	July 8, 2013
2	August 14, 2013
3	October 9, 2013
4	November 4, 2013
Labeling Meetings	
Labeling Planning Mtg	TBD
1	November 25, 2013
2	December 2, 2013
3	December 9, 2013
4	December 16, 2013
5	January 6, 2014
6	January 13, 2013
7	TBD

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):

	<p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ANISSA A DAVIS
05/22/2013

STACY R BARLEY
05/22/2013

BRIAN K STRONGIN
05/22/2013