CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205103Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA#	205103
Applicant Name	Aralez Pharmaceuticals
Date of Submission	March 14, 2016
PDUFA Goal Date	September 14, 2016
Proprietary Name / Established (USAN) Name	Yosprala/ aspirin/omeprazole
Dosage Forms / Strength	Tablet/ aspirin: 81 mg or 325 mg omeprazole 40 mg
Proposed Indication(s)	YOSPRALA, a combination of aspirin and omeprazole, is indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcer. The aspirin component of YOSPRALA is indicated for: • reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, • reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, • reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, • use in patients who have undergone revascularization procedures (Coronary Artery Bypass Graft [CABG] or Percutaneous Transluminal Coronary Angioplasty [PTCA]) when there is a pre-existing condition for which aspirin is already indicated. The omeprazole component of YOSPRALA is indicated for decreasing the risk of developing aspirin-associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (≥ 55) or documented history of gastric

	ulcers.
Action:	*Approval*

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

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

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

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

Division Director Review

1. Introduction

This is the third review cycle for this 505(b)(2) NDA for a fixed combination product (aspirin and omeprazole). The application was considered approvable by all review disciplines at the completion of the first review cycle, with the exception of the CMC reviewers due to a Withhold recommendation from the Office of Compliance. Deficiencies were found during the inspection of the (b) (4) Manufacturing facility, which supplied the aspirin drug substance for the product. The first CR letter was issued on April 25, 2014. A second CR letter was issued on December 16, 2014 due to continued facility deficiencies (b) (4) In this resubmission, the applicant proposes a new supplier for the aspirin drug substance (b) (4) The change in drug substance supplier for the aspirin component of this fixed combination product necessitated submission and review of new biopharmaceutical data and two relative BA/BE studies comparing the PK of the aspirin components of the two aspirin dose levels of the combination products produced in the original (b) (4) facility and the new (b) (4) facility.

2. Background

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

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

3. CMC

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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.