CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200671Orig1s000

SUMMARY REVIEW

Deputy Division Director Decisional Memo

Date	04 September 2015
From	Stephen M Grant
Subject	Deputy Division Director Decisional Memo
NDA/BLA #	200671
Applicant Name	New Haven Pharmaceuticals
Date of Submission	05 September 2014
PDUFA Goal Date	05 October 2015
Proprietary Name / Established (USAN) Name	DURLAZA/ aspirin
Dosage Forms / Strength	Extended release capsules/ 162.5 mg
Proposed Indication	To reduce the risk of cardiovascular events in patients with established cardiovascular disease
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of reviewers**
CMC Reviews	Lyudmila Soldatova
Biopharmaceutics Review	Sandra Suarez Sharp/ Kimberly Raines
Pharmacology Toxicology Review	Belay Tesfamariam
Clinical Pharmacology Reviews	Sudharshan Hariharan
Clinical Review	Fred Senatore
CDTL Review	Rajanikanth Madabushi
OSIS Memos	Hasan Irier
OSE/DMEPA Memos	Janine Stewart

OND = Office of New Drugs
CDTL = Cross-Discipline Team Leader
OSIS = Office of Study Integrity and Surveillance
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis

Introduction

Dr. Madabushi's CDTL memo ably reviews the background for and important issues presented by this application and can therefore serve as the summary basis of approval. In this memo, I will not summarize the information submitted by the applicant or the Agency reviews; I am in agreement with the conclusions of the review team. Rather I intend to highlight some issues germane to the approval and the use of this product.

Background

Aspirin (acetylsalicylic acid or ASA) has been used for decades for prevention of cardiovascular events such as cardiovascular (CV) death, myocardial infarction (MI), and stroke. The 1998 final rule for Internal Analgesic, Antipyretic and Anti-rheumatic Drug Products for OTC Human Use (63 FR 56802) provided professional labeling for aspirin and related products that included dosing and administration recommendations for the secondary prevention of CV events. The monograph for aspirin, which includes the approved indications, recommended doses, and a description of clinical studies can be found at 21 CFR 343.80.

Aspirin reduces the risk of adverse CV events through inhibition of platelet aggregation via irreversible acetylation of platelet cyclooxygenase-1 enzyme (COX-1). COX-1 is the rate-limiting enzyme in prostanoid biosynthesis, so that inhibition of COX-1 reduces prostanoid concentration. Inhibiting COX-1 in platelets prevents conversion of arachidonic acid to thromboxane A2 (TxA2), a prostanoid that is a potent stimulus of platelet aggregation and therefore of thrombosis.

However, aspirin's inhibition of COX-1 in other tissues results in actions that either are deleterious to the cardiovascular system or increase the risk of other serious adverse events. In vascular endothelium it reduces production of prostacyclin (PGI2), which relaxes smooth muscle and inhibits platelet aggregation. In the gastrointestinal (GI) tract COX-1 inhibition reduces production of PGE2 and prostacyclin, which protect the GI mucosa and reduce the risk of ulceration and bleeding.

DURLAZA was developed in an attempt to dissociate the favorable actions of aspirin on platelets from its unfavorable actions in the vascular endothelium and GI tract. A formulation of aspirin was developed that releases aspirin into the GI tract more slowly than other aspirin products. The hypothesis underlying the development of DURLAZA was that absorption of aspirin would be so slow that it would have the desired effect on platelets in the portal circulation but would be de-acetylated prior to reaching the systemic circulation. Hence systemic exposure would be minimal and aspirin would not have an effect on vascular endothelium and GI tract.

In this NDA the applicant, however, does not seek approval to market DURLAZA as safer or more effective than other aspirin products. To receive either of these claims evidence of superior safety or efficacy from clinical studies would be required. Rather the applicant seeks approval to market DURLAZA for the same cardiovascular claims included in the aspirin monograph, which requires only a demonstration of bioequivalence. The intended slow release of DURLAZA prevents approval based on pharmacokinetic bioequivalence to another aspirin product. The Division prospectively agreed that demonstration of pharmacodynamic (PD) bioequivalence would be acceptable evidence to support approval. The Division requested that the sponsor demonstrate that DURLAZA was equivalent to immediate-release (IR) aspirin in its effects on platelet aggregation and on the exposure to the stable metabolite of TxA2, TxB2.

Of some interest, the Division did not require the applicant to develop products bioequivalent to the entire range of doses of aspirin recommended in the monograph. The monograph generally recommends daily doses of 75 – 325 mg/day for secondary prevention of CV events. If the Division believed that there were identifiable patients that required doses as high as 325 mg, it might have required the applicant to develop an equivalent dose. It did not; it only required development of a dose equivalent to 81 mg of IR aspirin. Platelet COX-1 is completely inhibited by a dose of 81 mg. No other mechanism for aspirin's favorable effects

on CV outcomes has been definitively identified nor has it been demonstrated that any subgroup of patients have a greater CV benefit from higher doses of aspirin. The Division also implicitly accepts that doses of greater than 81 mg are not useful through its determination that trials requiring concomitant administration of doses less than 325 mg as required background therapy in CV outcome trials do not pose a risk to the subjects.

Outcomes

There are no CMC or Biopharmaceutics issues. Facility inspections are complete. The product will have a shelf-life of 15 months.

A single nonclinical study of gastrointestinal toxicity of a single dose of DURLAZA compared IR aspirin in rats was reviewed. IR aspirin at doses of 1670 and 2500 mg/kg were associated with upper GI lesions whereas doses of 2500 mg/kg of DURLAZA were not.

The clinical pharmacology information resulted in the following conclusions:

1. Administration of 162.5 mg of DURLAZA results in an approximately equivalent effect on TxB2 as 81 mg of IR aspirin, establishing PD equivalence and allowing the applicant to bridge to the information in the aspirin monograph. An OSIS memo raised some concerns about the utility of the assay employed. The applicant successfully responded to the concerns. However the applicant's response was submitted so close to the original PDUFA date that it necessitated extension of the review clock by three months to complete review of the submission.
2. The study intended to establish that 162.5 mg of DURLAZA results in an approximately equivalent effect on platelet aggregation as 81 mg of IR aspirin was underpowered and so did not demonstrate equivalence. It should be noted that the Division's experience with platelet aggregation assays is that they are difficult to perform and not very reliable. Various sponsors have suggested using some test of platelet aggregation to establish efficacy but the Division has not been persuaded to do so. However the establishment of equivalent effects on TxB2 exposure was judged adequate support.
3. Systemic exposure to aspirin was considerable, contrary to the applicant's hypothesis that the slow release in the GI tract would result in negligible exposure.
4. Administration of DURALAZA reduces urinary excretion of a prostacyclin metabolite, indicating that DURLAZA reduces prostacyclin activity and so is unlikely to be (b) (4) (b) (4)

Little useful clinical outcome information was submitted. What was submitted did not suggest that DURLAZA has any novel safety concerns. Of note, a 21-day crossover study in 23 healthy subjects conducted in 1996-97 (protocol number U5A-96-02-001) compared upper GI toxicity of DURLAZA at doses of 162.5 mg and 325 mg to 81 mg of enteric coated aspirin and 325 mg of IR aspirin. 22 and 16 subjects had gastric erosions detected at some time on upper endoscopy while on DURLAZA 162.5 and 325 mg, respectively. 16 and 20 had such erosions detected while on 81 of enteric coated aspirin and 325 mg of IR respectively. The number of erosions was greatest in subjects while on 325 mg IR aspirin and much fewer while on the other regimens. The incidence of hemorrhagic erosions was similar in all groups.

Labeling

The label for DURLAZA was based on the portions of the aspirin monograph (21CFR 343.80) pertinent to the cardiovascular claims but was revised to comply with PLR formatting requirements. The following notable edits were made:

1. The indication was modernized but not substantively changed. The indication includes a Limitation, unique to this formulation, that the slow release and absorption of DURLAZA makes it unsuitable for treatment of acute MI or (b) (4), conditions in which a rapid anti-platelet effect is required.
2. Sections 5 (Warning and Precautions) and 6 (Adverse Reactions) were revised from the Warnings and the Precautions sections of the monograph. Current labeling practices differ from those extant at the time the monograph was written. Lengthy lists of adverse events of questionable association with product administration are no longer included in contemporary labels. Current guidance on these sections state "To include an adverse event in the section, there should be reasonable causal association between the drug and the adverse event." Hence adverse reactions poorly documented or unlikely to be related to aspirin use have been deleted. (It should be noted that the sensible approaches to labeling taken by the Division's Safety Deputy, Mary Ross Southworth, and the Associate Director for Labeling, Michael Monteleone, were applied to good effect in these sections.)
3. The clinical studies section was succinctly summarized.

Overall the DURLAZA label represents a clearer, more concise version of the aspirin monograph and is therefore an improvement.

Action

The clinical information submitted by the applicant does not suggest that, compared to the effect of aspirin available over-the-counter, the effect of DURLAZA on the GI tract and on prostacyclin production by the vascular endothelium is different. In fact, the information tends to suggest there is no clinically relevant difference. However, the applicant has submitted the necessary information to establish a bridge to the information in the aspirin monograph and so DURLAZA will be approved for the cardiovascular indications contained in the monograph.

There are no post-marketing commitments or requirements.

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/s/

STEPHEN M GRANT
09/04/2015