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*APPLICATION NUMBER:*

**200671Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	September 28, 2015
<b>From</b>	Rajanikanth Madabushi, Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	200671
<b>Type</b>	505(b)(2)
<b>Applicant</b>	New Haven Pharmaceuticals, Inc.
<b>Date of Submission</b>	September 05, 2014
<b>PDUFA Goal Date</b>	October 05, 2015 (extended from July 05, 2015 due to Major Amendment on June 26, 2015)
<b>Proprietary Name / Established (USAN) names</b>	DURLAZA® [acetylsalicylic acid (ASA)]
<b>Dosage forms / Strength</b>	Controlled Release Capsules - 162.5 mg
<b>Proposed Indication(s)</b>	Secondary prevention of cardiovascular events
<b>Recommended Action:</b>	<b>Approval</b>

This secondary review is based, on the primary reviews/memorandums of:

- OSIS (Srinivas Rao Chennamaneni), 02/05/2015
- OSIS (Hasan A Irier), 06/18/2015
- OMEPRM (Kellie A Taylor), 11/21/2014
- DMEPA (Janine Stewart), 03/16/2015
- PeRC Meeting Minutes (George E Greely), 05/26/2015
- Chemistry ( Lyudmila N Soldatova), 02/09/2015, 04/29/2015
- Biopharmaceutics (Sandra Suarez Sharp and Kimberly Raines) 04/05/2015
- Pharmacology/Toxicology (Belay Tesfamariam), 04/24/2015
- Clinical (Fred Senatore), 04/30/2015
- Clinical Pharmacology (Sudharshan Hariharan), 06/02/2015 and 08/08/2015

## Cross Discipline Team Leader Review

### 1. Introduction

In the current submission (NDA 200671), New Haven Pharmaceuticals Inc., is seeking authorization to market Durlaza<sup>®</sup>, a microencapsulated controlled release aspirin product, for the secondary prevention of cardiovascular events, pursuant to the requirements of section 505(b)(2) of the Federal Food, Drug and Cosmetics Act, 21 CFR 314. Aspirin and several aspirin containing products (21CFR 343.90) are available in the United States as over-the-counter (OTC) products. Per 21 CFR 343.12 Aspirin and Buffered Aspirin are identified as cardiovascular active ingredients. The professional labeling for aspirin and aspirin containing products is described under 21 CFR 343.80. Durlaza<sup>®</sup> is a new dosage form of aspirin, as such a 505(b)(2) pathway is a viable regulatory pathway. The Applicant is relying on the publicly available data in the OTC aspirin monograph and the professional labeling in 21 CFR 343.80 for efficacy and safety data. In support of this efficacy and safety reliance, the Applicant conducted a dose-response study that serves as the pivotal bridge to the monograph.

### 2. Background

Unless contraindicated, aspirin 75 mg – 162 mg daily is recommended (Class I; Level of Evidence: A) for secondary prevention in patients with coronary artery disease<sup>1</sup>. Aspirin is an irreversible platelet inhibitor. It exhibits the antiplatelet activity via irreversible acetylation of the cyclooxygenase-1 (COX-1) on the platelets. Inhibition of COX-1 prevents conversion of arachidonic acid to thromboxane A<sub>2</sub> (TxA<sub>2</sub>), which a potent agonist of platelet aggregation and therefore of thrombosis. At doses of 75 – 81 mg mg daily, near maximal inhibition of TxA<sub>2</sub> is observed. However, at higher doses, aspirin is reported to inhibit the synthesis of vasodilatory prostaglandins such as PGE<sub>2</sub> and PGI<sub>2</sub>. Therefore higher doses may not provide additional protection against the risk of heart attacks and stroke but may cause more gastrointestinal bleeding. The Applicant developed Durlaza<sup>®</sup> with an intention to deliver low, continuous exposure of acetylsalicylic acid (ASA) sufficient to block platelets in the portal vein from synthesizing TxA<sub>2</sub>. With this approach the Applicant expected minimal ASA levels in the systemic circulation such that the beneficial production of prostacyclin and other prostaglandins may not be impeded.

#### Regulatory History:

The drug product was originally developed by Flamel Technologies, France under the brand name Asacard<sup>®</sup>. Asacard<sup>®</sup> 162.5 mg was approved by the European Medical Agency in 1998 for secondary prevention of CV disease, but was never marketed in any country. The rights to the product were obtained by New Haven Pharmaceuticals. The Applicant explored a 505(b)(2) regulatory strategy for seeking approval of Durlaza<sup>®</sup> in the United States based on pharmacodynamic equivalence to standard immediate release aspirin. The Applicant stated

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<sup>1</sup> AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update.



## 4. Nonclinical Pharmacology/Toxicology

In the current submission the Applicant submitted a single dose toxicology study comparing the acute gastrointestinal (GI) toxicity of Durlaza<sup>®</sup> to the standard aspirin oral formulation in rats. The previously approved ASA studies are referenced to describe the pharmacology, pharmacokinetics, general toxicology, genotoxicity, carcinogenicity and reproductive toxicology. The pharmacology/toxicology reviewer reports the following findings from the single study:

- At a dose of 2500 mg/kg, Durlaza<sup>®</sup> showed no pathological lesions in the stomach. This dose represents several orders of magnitude higher than the clinical dose of Durlaza<sup>®</sup> (162.5 mg ; 2.7 mg/kg).
- The Standard aspirin showed macroscopic evidence of GI toxicity including red petechiae, discoloration and thickening of the stomach wall at oral gavage dosages of  $\geq 1670$  mg/kg.
- Some limitations of the study are that indices of aspirin bioavailability, platelet cyclooxygenase-1 (COX-1) activity, and PGI<sub>2</sub> biosynthesis (6-keto-prostaglandin F1 $\alpha$ ) were not measured.

The Pharmacology/Toxicology reviewer concludes that Durlaza<sup>®</sup> showed a safe profile in the gastrointestinal tract.

## 5. Clinical Pharmacology

The Applicant submitted data from eight clinical pharmacology studies conducted in healthy subjects and one study in patients with atherosclerotic disease. The clinical pharmacology reviewer states that only three studies are deemed essential for supporting the regulatory action and inform labeling of Durlaza<sup>®</sup>. The Study NHP-ASP\_01 is a pivotal dose finding study, the effect of food on Durlaza<sup>®</sup> was evaluated in Study ASA-001 and lastly the study CLICR-30 was a comparative study of the effect on the production of vascular and platelet prostaglandin of the controlled release aspirin versus immediate release aspirin in healthy volunteers. Detailed description of these studies can be found in the clinical pharmacology review. The clinical pharmacology reviewer concludes that the bridging information from the study NHP-ASP-01 is acceptable and recommends approval of Durlaza<sup>®</sup> at a dose of 162.5 mg. No agreement has been reached with Applicant about final labeling.

The key findings are briefly described below:

1. The relative bioavailability of ASA following Durlaza<sup>®</sup> administration is 37% when compared to IR aspirin (ratio of AUC<sub>0-last</sub> geometric means between Durlaza<sup>®</sup> 81 mg and IR aspirin 81 mg). The C<sub>max</sub> of ASA following Durlaza<sup>®</sup> 81 mg is 23% of IR aspirin 81 mg.
2. The systemic exposure to ASA following the administration of Durlaza<sup>®</sup> 162.5 mg is ~70% of that achieved by IR aspirin 81 mg. The C<sub>max</sub> is ~35% of that achieved by IR aspirin 81 mg. The apparent elimination half-life of ASA following the administration of Durlaza<sup>®</sup> 162.5 mg is 120 minutes compared to ~40 minutes with IR aspirin 81 mg. These PK characteristics support the extended release characteristics of Durlaza<sup>®</sup>.
3. The dose-response (platelet COX-1 activity) study shows that aspirin displays an E<sub>max</sub> relationship. While the maximum inhibition of serum TxB<sub>2</sub> at 24 hrs

- (represents the time of maximum effect following single dose) is similar for Durlaza<sup>®</sup> and immediate release aspirin, the dose required to achieve half-maximal inhibition (ED<sub>50</sub>) with Durlaza<sup>®</sup> is 1.9-fold higher relative to IR aspirin. With urinary 11-dehydro-TxB<sub>2</sub> as the response marker, the ED<sub>50</sub> of Durlaza<sup>®</sup> was 2.3-fold higher compared to IR aspirin. Based on this information, a dose of Durlaza<sup>®</sup> 162.5 mg can be considered to achieve antiplatelet effect effects similar to that achieved by IR aspirin 81 mg.
4. Pairwise data comparison indicates that the mean inhibition of serum TxB<sub>2</sub> following the first dose of Durlaza<sup>®</sup> 162.5 mg is lower than that observed following IR aspirin 81 mg. However, upon repeat administration of Durlaza<sup>®</sup> 162.5 mg, the inhibition of serum TxB<sub>2</sub> reaches near maximal values by Day 4. Due to time taken to reach maximum pharmacodynamic effect, the proposed label includes a warning not to administer Durlaza<sup>®</sup> when a rapid onset of action is required (e.g., acute treatment of MI or (b) (4)).
  5. Inhibition of platelet aggregation at 24 hours post-dosing using arachidonic acid as the agonist was binary, with values either inhibited by >90% or near baseline. This results in high variability and as such there was not enough power to conduct a conventional dose-response analysis. Of note, Durlaza<sup>®</sup> doses of 162.5 mg, 325 mg and IR aspirin 81 mg were the only dose levels that showed some inhibition values >90%. This information generally consistent with that observed for inhibition of serum TxB<sub>2</sub> and urinary urinary 11-dehydro-TxB<sub>2</sub> and can be considered supportive of the primary findings.
  6. A high fat meal has been shown to further prolong the absorption of ASA from the drug product resulting in a delayed T<sub>max</sub> (median = 4.0 h), modest increase in C<sub>max</sub> (1.4-fold) and approx. 3-fold higher AUC, compared to when administered under fasted condition. The increase in exposure to ASA in the presence of a high fat meal is ~ 2-fold higher when compared to exposures resulting from IR aspirin 81 mg. Though there is clinical experience with ASA exposures of this magnitude, however, the study findings indicate alteration of the extended release characteristics of the product. Further, it is not clear whether the findings with a high-fat meal can be extrapolated to different meal types. Therefore, Durlaza<sup>®</sup> should preferably be administered in a fasted state.
  7. There is no evidence of (b) (4) for Durlaza<sup>®</sup> as claimed by the Applicant. There is no difference in urinary 6-keto-PGF<sub>1α</sub> levels between Ascard<sup>®</sup> (extended release product similar to Durlaza<sup>®</sup>) and Kardegic<sup>®</sup> 162.5 mg (immediate release product of aspirin) treatment groups following once-daily administration for 10 days.
  8. When concomitant use with ibuprofen is warranted, ibuprofen should be administered at least 2 to 4 h after Durlaza<sup>®</sup> dosing. Also, at least 8 h should elapse after ibuprofen dosing, before administering aspirin, to avoid significant interference. When twice-a-day or more frequent regimen for ibuprofen is warranted, this combination may not be used together. This is consistent with the drug safety communication issued by FDA in 2006 alerting health care professions about the interaction potential between low dose aspirin and ibuprofen.

## 6. Clinical Microbiology

There are no specific clinical microbiology issues in the current submission.

## 7. Clinical/Statistical Efficacy

There is no efficacy data submitted with this submission. The submission relies on the efficacy of OTC aspirin for the secondary prevention of acute cardiovascular events. The Applicant has provided the necessary bridging information that allows for reliance on OTC aspirin for the efficacy findings as allowed under the 505(5)(2) of the Food, Drugs and Cosmetics (FDC) Act (see Section 5 and Clinical Pharmacology Review for details). As such there is no additional Clinical or Statistical evaluation of efficacy for this submission.

## 9. Safety

In a double-blind crossover study in healthy volunteers designed, after 21 days of treatment with Durlaza<sup>®</sup>, 96% (22/23; 8 of which were hemorrhagic) of the subjects were reported to have erosions on endoscopy as compared to 70% (16/23; 5 of which were hemorrhagic) subjects on IR aspirin (75 mg). Further, once ulcer was detected in the gastric antrum of each of 2 subjects at 7 and 14 days after treatment with Durlaza<sup>®</sup>. This finding is contrary to the applicant's expectation of a gastro-protective effect with Durlaza<sup>®</sup> compared to an equivalent dose of IR aspirin.

Since most of the studies conducted by the applicant were in healthy volunteers, traditional safety analyses could not be performed. Therefore, safety of Durlaza<sup>®</sup> was evaluated by reviewing 15 clinical trials (1 pivotal and 14 legacy). Doses ranged from 20 mg to 1300 mg. The doses of the active comparator, immediate release aspirin, ranged from 5 mg to 1200 mg. Durations of therapy ranged from a single dose to daily doses of up to 7 months. Data from the pooled analyses seem to (for details see the Clinical Review by Senatore) indicate that the adverse event rate, serious adverse event rate and gastrointestinal adverse event rate were numerically lower for the Durlaza<sup>®</sup> groups compared to the IR aspirin groups. There are limitations of integrating adverse events from legacy trials conducted in 1990s, along with pooling of data from healthy subjects (b) (4)

Despite these limitations, it is reasonable to only conclude that there were no new empirical safety signals for Durlaza<sup>®</sup> relative to immediate release aspirin as stated by the Clinical Reviewer (for details see Clinical Review by Senatore) (b) (4)

## 10. Advisory Committee Meeting

An Advisory Committee Meeting was deemed unnecessary because the application did not present novel issues or difficulties in the interpretation of study results.

## 11. Pediatrics

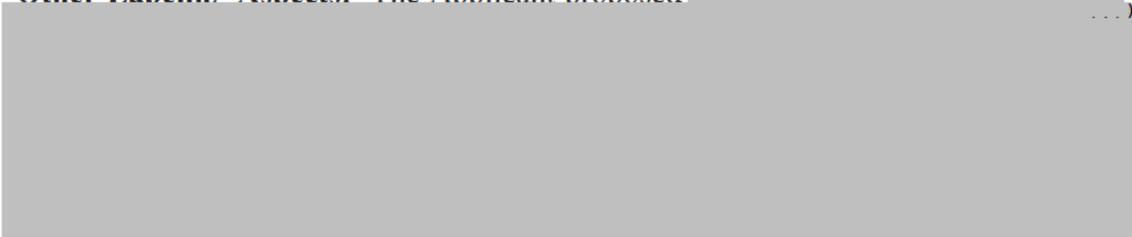
The Applicant requested a full waiver of pediatric studies for this application. In their Agreed-Upon Pediatric Study Plan (Agreed iPSP), the Applicant states that the incidence of thrombus mediated cardiovascular events in pediatric population is extremely low, thus rendering the determination of efficacy and safety impractical (see IND 116348, 12/19/2014). Further, Durlaza<sup>®</sup> 162.5 mg, like immediate release aspirin is intended for secondary prevention of cardiovascular events and not for primary prevention. The Division concluded that the Applicant's rationale for seeking full waiver reasonable and confirmed agreement to the Applicant's Agreed iPSP in an Advice Letter (dated 02/09/2015). The Pediatric Review Committee (PeRC) reviewed the full waiver request and agreed with iPSP (see PeRC Meeting Minutes dated 05/13/2015).

## 12. Other Relevant Regulatory Issues

- **Financial disclosures:** There are no issues related to financial disclosure.
- **Clinical Inspection Summary:** Inspections for two analytical sites that provided the pivotal dose-response information from Study NHP-ASP-01 was requested by the Clinical Pharmacology Reviewer. At the (b) (4), (b) (4), the assays to be inspected are serum thromboxane B2, urine-11-dehydrothromboxane, and plasma acetylsalicylic acid and salicylic acid. At the second site, (b) (4) platelet aggregation assay using arachidonic acid and collagen as agonists were to be inspected.
  - In a memorandum (dated: 02/05/2015), the Office of Study Integrity and Surveillance (OSIS) recommended to accept data without on-site inspection for (b) (4). The reason in support of the recommendation is that this site was inspected twice in the last two years and no significant observations were identified during these inspections.
  - The OSIS inspection of the (b) (4) found limitations (review DARRTS date: 06/18/2015). The inspection identified cross-reactivity with structurally similar analogs in the ELISA method used for bioanalysis of serum thromboxane B2 (TxB2) and urinary 11-dehydro-TxB2. The OSIS review concluded that their findings may affect the ability to interpret pharmacodynamic data from study NHP-ASP-01. These findings were communicated to the applicant. On June 26, 2015, the applicant responded by providing evidence from literature making a case that the identified issues do not affect the ability to interpret the study results. This new information was considered as a major amendment and resulted in extending the goal date by three months to provide time for a full review of the submission (see Review Extension – major Amendment; DARRTS date 06/30/2015).
  - In the submission the applicant states that the cross-reactivity to 2, 3-dinor TxB2 and 11-dehydro-2, 3-dinor TxB2 should not significantly impact the pharmacodynamics response to aspirin as they were downstream metabolites of TxB2 and as such accounted for the antiplatelet activity. The applicant

further stated that the cross-reactivity to TxB3 is expected to be minimal as this is identified to be significant in diet constituting a significant amount of fish oil. According to the applicant the diet of study participants did not constitute a significant amount of fish oil. Lastly, the applicant states that the issue of cross-reactivity if any should affect both reference and test arms to the same extent and as such the comparison is unaffected. The Clinical Pharmacology team reviewed this information and concludes that cross-reactivity with the ELISA method for bioanalysis of serum TxB2 and urinary 11-dehydro-TxB2 does not significantly impact the results of study NHP-ASP-01 (Addendum to Clinical Pharmacology Review; dated: 08/08/25).

### 13. Labeling

- **Proprietary Name:** The proposed proprietary name Durlaza<sup>®</sup> has been reviewed by the Office of Medication Error Prevention and Risk Management (see Correspondence dated 11/21/2014) and is found conditionally acceptable.
- **Risk Assessment:** The Division of Medication Errors Prevention and Analysis has performed a risk assessment of the proposed Prescribing Information, the container labels and carton labeling that may lead to medication errors and areas for improvement and has recommendations to increase clarity, readability and the prominence of important information to promote the safe use of Durlaza<sup>®</sup> (for details, see Safety Labeling Review by Stewart). These were conveyed to the Applicant in a General Advice letter on 03/16/2015.
- **Other Labeling Aspects:** The Applicant proposed (b) (4)  


### 14. Recommendations

Based on the review of information submitted to the application, I believe that an appropriate bridge between Durlaza<sup>®</sup> 162.5 mg and IR aspirin 81 mg has been established. This allows for reliance on the safety and efficacy for secondary prevention of cardiovascular events previously established under the Aspirin OTC Monograph. Pending an agreement to the final labeling, I recommend **Approval** as the appropriate regulatory action for this application.

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/s/  
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RAJANIKANTH MADABUSHI

08/28/2015

CDTL Review