

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200671Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA: 200671
IND: 116348
Drug: DURLAZA (aspirin) Extended Release Capsules
Class: Non-Steroidal Anti-Inflammatory Drug (NSAID)
Applicant: New Haven Pharmaceuticals
Proposed Indication: DURLAZA is a Nonsteroidal Anti-inflammatory Drug indicated for:

- (b) (4)
- Reduce the (b) (4) risk of death and (b) (4) stroke in patients who have had ischemic stroke or transient (b) (4)
 - Reduce the (b) (4) risk of death and (b) (4) myocardial infarction (MI) in patients with a (b) (4) MI or unstable angina pectoris
 - (b) (4) with chronic stable angina (b) (4)

(b) (4)

(b) (4) **Limitations:** DURLAZA (b) (4) not (b) (4) in situations where a rapid onset of action is required (such as acute treatment of myocardial infarction or (b) (4)).

Date of Submission: 5 September 2014
Original PDUFA: 5 July 2015
Major Amendment: 30 June 2015
New PDUFA Date: 5 October 2015

❖ **REVIEW TEAM**

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
 - Cross-Discipline Team Leader (CDTL)
 - Raj Madabushi, PhD
 - Medical Reviewers
 - Fortunato Senatore, MD, PhD

- Pharmacology/Toxicology Reviewer
 - Belay Tesfamariam, PhD
- Regulatory Project Manager
 - Alison Blaus, RAC
- Office of Clinical Pharmacology
 - Sudharshan Hariharan, PhD
- Office of New Drug Quality Assessment (ONDQA)
 - Lyudmila Soldatova, PhD (Drug Substance / Drug Product)
 - Sandra Suarez, PhD (Biopharmaceutics)
- Office of Surveillance and Epidemiology
 - Janine Stewart, PharmD (DMEPA)
- Office of Medical Policy Initiatives, Division of Medical Policy Programs, Patient Labeling
 - Karen Dowdy, RN, BSN (Reviewer)

❖ **BACKGROUND**

Durlaza is a controlled release aspirin product (b) (4) and being developed in the USA by NHP. On 10 December 2009 and 23 November 2010 (minutes dated 28 December 2009 and 2 December 2010 respectively) the sponsor attended a pre-NDA meeting (under NDA 200671) where a number of agreements were made, among them the sponsor's acceptance of the Agency's requirement that they conduct the dose-PD response (thromboxane B2 and platelet aggregation inhibition) study entitled, "A Phase 1 Open-label, Four-way, Randomized, Crossover, Single-Dose, Dose-Response Study Comparing the Pharmacodynamic of Micropump® Aspirin Capsules to Immediate-Release Aspirin Capsules in Healthy Volunteers". They also agreed to provide long-term stability testing covering a minimum of 12 months duration on at least three primary batches. In lieu of a third pre-NDA meeting, preliminary comments were sent to the sponsor and those are dated 30 August 2013.

❖ **REGULATORY TIMELINE and GENERAL APPLICATION POINTS**

This section will cover a number of clinical development and general application milestones (pre- and post-NDA submission). The review of this application proceeded relatively smoothly, with approximately 22 information requests since 5 September 2014.

- Pre-NDA Meeting: 10 December 2009 (Minutes dated - 28 December 2009 – Further studies recommended that were to be conducted under an IND)
- Pre-NDA Meeting Follow-up: 23 November 2010 (Minutes dated 2 December 2010)
- Pre-IND Meeting: 13 November 2012 (Preliminary Comments dated 6 November 2012 – Meeting Cancelled)
- IND received: 28 March 2013
- Pre-NDA Meeting: 10 September 2013 (Preliminary Comments dated 30 August 2013 – Meeting Cancelled)
- NDA Submission Received: 5 September 2014
- Filing Meeting: 27 October 2014
- 74-day Issues Letter with Comments: 19 November 2014
- Mid-Cycle Meeting: 2 February 2015
- Major Amendment: 30 June 2015
- Approval Letter: 4 September 2015

User Fee

The user fee for this application was waived prior to the submission of the application (ID 2014.062).

Pediatric Review Committee (PeRC)

The PeRC meeting to discuss this application was held on 13 May 2015. The PeRC and the Division agreed with the applicant that this indication would be highly impractical to pursue in the pediatric population since the condition is extremely rare. Therefore, a full pediatric waiver was granted for this application.

Advisory Committee

There was no advisory committee for this application as this is a 505(b)(2) relying upon a previously approved product (aspirin) and there were no review issues that warranted input from the committee.

Trade name

DURLAZA was deemed conditionally acceptable on 21 November 2014.

Review Status

This 505(b)(2) was granted a standard review, not under “The Program”. Therefore, this application had a 10-month clock.

❖ **LABELING REVIEW**

Labeling was first sent to the applicant on 4 June 2015 and went through approximately 4 rounds of negotiations. The label was agreed-upon on 26 June 2015 and is appended to the Approval Letter.

Medication Guide

Although the applicant voluntarily submitted a Medication Guide as part of labeling for this NDA, the risks of this product appear commensurate with those associated with other available forms of aspirin, which do not have Medication Guides. Therefore, a Medication Guide was not deemed necessary.

❖ **DISCIPLINE REVIEWS**

Below are the conclusions reached by the DURLAZA team members, organized by role and/or discipline.

Divisional Memorandum (4 September 2015)

Dr Grant drafted and finalized a review from the Division on 4 September 2015 concurring with the primary reviewers and CDTL recommending approval.

Cross-Discipline Team Leader (CDTL) Review (28 August 2015)

Dr. Madabushi drafted and finalized a review from the Division on 28 August 2015 concurring with the primary reviewers recommending approval.

Clinical Reviews (dated 30 April 2015)

Dr. Senatore recommended approval Durlaza for the indications listed in the aspirin monograph. The basis of his recommendation was: 1) There is pharmacodynamic equivalence between DURLAZA and immediate release aspirin regarding inhibition of thromboxane synthesis and inhibition of platelet aggregation, as determined by the Office of Pharmacology 2) No empirical pharmacodynamic effect on prostacyclin suggesting a safety signal, based on legacy studies 3) No safety signals relative to immediate release aspirin.

Clinical Pharmacology Review (dated 2 June 2015 and 8 August 2015)

Dr. Hariharan from the Office of Clinical Pharmacology (OCP/DCP1) found the bridging information from Study NHP-ASA-01 acceptable as well as the applicant’s response to the Office of Scientific Investigations (OSI) findings of their inspection of the bioanalytical site. Dr. Hariharan recommended approval of DURLAZA 162.5 mg.

❖ **CONSULT REVIEWS**

Please see the following consults that were requested during the NDA review and the corresponding date they were finalized:

- OSI (Clinical Audit): Not Applicable (No clinical trials that were critical to the application's approval)
- OSI (Bioanalytical Inspection): 5 February 2015 and 18 June 2015
- DMEPA (Tradename): 6 November 2014
- DMEPA (Carton-Container Labeling): 16 March 2015 and 15 June 2015
- DRISK (REMS): Not Applicable
- Patient Labeling (Medication Guide): 25 June 2015
- Office of Prescription Drug Promotion (OPDP): 22 June 2015

❖ **CONCLUSION**

After taking into consideration all of the primary reviews, consults, and the applicant's additional analyses, the Agency issued an Approval Letter for NDA 200671 on 4 September 2015.

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/s/

ALISON L BLAUS
09/04/2015

505(b)(2) ASSESSMENT

Application Information		
NDA # 200671	NDA Supplement #: S- n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: DURLAZA Established/Proper Name: aspirin Dosage Form: Extended Release Capsules Strengths: 162.5 mg		
Applicant: New Haven Pharmaceuticals		
Date of Receipt: 5 September 2014		
PDUFA Goal Date: 5 October 2015 (Major Amendment submitted extending the clock 3-months from 5 July 2015)		Action Goal Date (if different):
RPM: Alison Blaus, RAC		
Proposed Indications: <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> <ul style="list-style-type: none"> • Reduce the (b) (4) risk of death and (b) (4) stroke in patients who have had ischemic stroke or transient (b) (4) • Reduce the (b) (4) risk of death and (b) (4) myocardial infarction (MI) in patients with a (b) (4) MI or unstable angina pectoris <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> (b) (4) with chronic stable angina (b) (4)		
(b) (4)		
(b) (4) Limitations: DURLAZA (b) (4) not (b) (4) in situations where a rapid onset of action is required (such as acute treatment of myocardial infarction or (b) (4)).		

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)
United States Aspirin Monograph, Professional Labeling, Code of Federal Regulations, Title 21, Part 343 (Internal Analgesic, Antipyretic, and Antirheumatic Drugs for Over-The-Counter Human Use)	All sections of the labeling are based on the monograph, with the exception of Sections 2, 3, 11 and 12.

*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 sponsor conducted study NHP-ASA-01 which was a pivotal dose-response study that was performed to choose a dose of NHP-55C that is pharmacodynamically equivalent to controlled release aspirin 81 mg. The response measures selected were inhibition of serum TxB₂, inhibition of urinary 11-dehydro-TxB₂, and inhibition of platelet aggregation. Based on the data from that study, the clinical pharmacology reviewer determined that based on a 2-fold lower ED50, NHP-554C 162.5 mg should be pharmacodynamically equivalent to IR aspirin 81 mg. Please see the finalized clinical pharmacology review by Sudharshan Hariharan for a more in depth review of this study.

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).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

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)

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:

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:

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").

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 numbers:

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):

- 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 numbers:

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

Patent number(s):

Expiry dates:

- 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):
- (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):

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

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/s/

ALISON L BLAUS
07/21/2015

**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: June 24, 2015

To: Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products (DCRP)

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)
Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: (b) (4)

Drug Name (established name): DURLAZA (aspirin)

Dosage Form and Route: Extended Release Capsules, for oral use

Application Type/Number: NDA 200671

Applicant: New Haven Pharmaceuticals, Inc.

1 INTRODUCTION

On September 5, 2014, New Haven Pharmaceuticals, Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 200671 for DURLAZA (aspirin) Extended Release Capsules with the proposed indications:

- (b) (4)
- Reduce the (b) (4) risk of death and (b) (4) stroke in patients who have had ischemic stroke or transient (b) (4)
 - Reduce the (b) (4) risk of death and (b) (4) MI in patients with a (b) (4) MI or unstable angina pectoris (b) (4) with chronic stable angina (b) (4)

(b) (4)

The specific indications, as well as other components of the proposed product labeling not specific to DURLAZA, are modeled after the US Nonprescription Aspirin Monograph, Professional Labeling.

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 Cardiovascular and Renal Products (DCRP) on September 22, 2014, for DMPP and OPDP to review the Applicant's proposed (b) (4) for DURLAZA (aspirin) Extended Release Capsules.

2 MATERIAL REVIEWED

- Draft DURLAZA (aspirin) Extended Release Capsules (b) (4) received on September 5, 2014, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on June 10, 2015.
- Draft DURLAZA (aspirin) Extended Release Capsules Prescribing Information (PI) received on September 5, 2014, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on June 10, 2015.

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 (b) (4) 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the (b) (4) document using the Arial font, size 10.

In our collaborative review of the (b) (4) we have:

- simplified wording and clarified concepts where possible
- ensured that the (b) (4) is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the (b) (4) is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the (b) (4) meets the Regulations as specified in 21 CFR 208.20
- ensured that the (b) (4) meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The (b) (4) 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 (b) (4) 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 (b) (4).

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
06/24/2015

ZARNA PATEL
06/24/2015

MARCIA B WILLIAMS
06/24/2015

LASHAWN M GRIFFITHS
06/25/2015

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

Memorandum

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

Date: June 22, 2015

To: Alison Blaus, RAC
Senior Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

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

Subject: **Durlaza (aspirin) extended release capsules**
NDA: 200671
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on September 22, 2014, for Durlaza (aspirin) extended release capsules. OPDP's comments are provided directly on the attached copy of the substantially complete PI emailed to us on June 10, 2015.

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

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
06/22/2015

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: June 17, 2015

TO: Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation-I
Office of New Drugs

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

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Director (Acting)
Division of Generic Drugs Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Science

SUBJECT: Review of EIR covering the analytical portions of
studies submitted in support of NDA 200671.

At the request of the Office of New Drugs, the Office of Study Integrity and Surveillance (OSIS), Division of Generic Drugs Bioequivalence Evaluation (DGDBE) conducted an inspection of the analytical portions of the following study at (b) (4)

(b) (4)

Study Number: NHP-ASP-01

Study Title: "A phase 1, open-label, four-way, randomized, crossover, single-dose, dose-response study comparing the pharmacodynamics and pharmacokinetics of NHP-554C capsules to

immediate release aspirin capsules in healthy
volunteers"

Study Conduct Dates: JUL 23, 2013 to August 06, 2013.

Hasan A. Irier, Ph.D. (Pharmacologist, DGDBE/OSIS) audited data of the study NHP-ASP-01 at (b)(4) between (b)(4). The audit included a thorough review of study records, examination of facilities and equipment, and interviews and discussions with the firm's management and staff. During the audit of analytical portions of study NHP-ASP-01, objectionable conditions were observed. At the conclusion of the inspection at (b)(4), Dr. Irier issued Form FDA-483 (**Attachment 1**) to the firm, and presented a list of discussion items. DGDBE received a written response to the inspectional findings from (b)(4) on April 30, 2015 (**Attachment 2**). DGDBE evaluations of the observations and the firm's responses are discussed below:

FDA-483 observations:

(b)(4)

(b) (4)



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

ATTACHMENTS:

1. FDA Form 483, and Inspection Memo NDA 200671
2. Firm's Response to FDA Form-483
3. Thromboxane B2 (b) (4) Kit (Cat. No. (b) (4))
4. Thromboxane B2 (b) (4) Kit (Cat. No. (b) (4))

Final Classification:

VAI - (b) (4)

DARRTS CC:

OSI/DBGLPC/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Cho/Irier
/Dejernett/Nkah/Fenty-Stewart/Johnson
CDER/OND/ODEI/DCRP/Jenkins/Blaus

Draft: HAI 05/04/2015, 06/17/15
Edits: YMC 6/17/2015; SHH 6/18/2015

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/

OSIS: File#: BE6793

FACTS: (b) (4)

Hasan Irier -A
Digitally signed by Hasan Irier -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Hasan Irier -A,
0.9.2342.19200300.100.1.1=2001568214
Date: 2015.06.18 10:39:02 -04'00'

Sam H. Haidar -S
Digitally signed by Sam H. Haidar -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Sam H. Haidar -S,
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Date: 2015.06.18 11:09:38 -04'00'

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/s/

HASAN A IRIER
06/18/2015

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: June 15, 2015
Requesting Office or Division: Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number: NDA 200671
Product Name and Strength: Durlaza (Aspirin) Extended Release Capsules,
162.5 mg
Submission Date: March 27, 2015
Applicant/Sponsor Name: New Haven Pharmaceuticals Inc.
OSE RCM #: 2014-1965-1
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular & Renal Products (DCRP) requested that we review the revised container labeling and carton 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 labeling and carton labels are acceptable from a medication error perspective.

¹ Stewart J. Label and Labeling Review for Durlaza (NDA 200671). 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); 2015 March 16. 13 p. OSE RCM No.: 2014-1965.

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/s/

CHI-MING TU
06/15/2015

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:	March 16, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 200671
Product Name and Strength:	Durlaza (aspirin) Extended Release Capsules 162.5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	New Haven Pharmaceuticals Inc.
Submission Date:	December 10, 2014, February 16, 2015, February 23, 2015, and February 24, 2015
OSE RCM #:	2014-1965
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the 505 (b)(2) NDA review for Durlaza (aspirin) Capsules, this review evaluates the proposed container labels, carton labeling, and Prescribing Information for areas of vulnerability that can lead to medication errors. The reference listed drug (RLD) for this 505(b)(2) NDA as cited by the Applicant is the United States Aspirin Monograph¹.

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
FDA Adverse Event Reporting System (FAERS)	B- N/A
Previous DMEPA Reviews	C- N/A
Human Factors Study	D- N/A
ISMP Newsletters	E- N/A
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 Prescribing Information, the container labels and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We note the NDC number is omitted from the appropriate section of the Prescribing information. We note a C-shaped graphic that competes with the prominence of critical product information. Further, we note the statement pertaining to the contents of each capsule is inconsistently expressed on the side panels of the container labeling and carton labels and in the Prescribing Information. In addition, we note product information on the container labels and carton labeling can be revised to promote the safe use of the product.

¹ United States Aspirin Monograph, Professional Labeling, Code of Federal Regulations, Title 21, Part 343 (Internal Analgesic, Antipyretic, and Antirheumatic Drugs for Over-The-Counter Human Use) Revised as of April 1, 2013.

CMC has identified labeling issues requiring clarification and revision including the established name and the equivalency statement. Their comments were forwarded to the Applicant as an Information Request.

Thus, we provide our recommendations to mitigate confusion and promote the safe use of this product in Section 4.

4 CONCLUSION & RECOMMENDATIONS

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

4.1 RECOMMENDATIONS FOR THE DIVISION

General Comment

1. We defer to CMC for determination of the equivalency statement. The equivalency statement in the PI is presented as “ (b) (4) 162.5 mg of aspirin (b) (4) whereas it is presented on the container label and carton labeling as “Each capsule contains 162.5 mg of (b) (4) Aspirin”.

Prescribing Information

1. In the *Dosage and Administration* sections of the *Highlights of Prescribing Information* and in the *Full Prescribing Information*, add a statement similar to (b) (4) (b) (4) to be consistent with the information provided in the Medication Guide.
2. In Section 16: How Supplied/Storage and Handling, add the NDC numbers to appear adjacent to the corresponding package configurations.

4.2 RECOMMENDATIONS FOR NEW HAVEN PHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this NDA:

Container Label and Carton Labeling (including professional sample)

1. Remove the (b) (4) from the principal display panel (PDP). Critical information such as the proprietary name, established name, and strength should be the most prominent information on the PDP. Other information such as the (b) (4) (b) (4) should not compete in size and prominence with critical product information.²
2. The established name lacks prominence commensurate with the proprietary name. Thus we request you revise the presentation of the entire established name “(Aspirin) Extended Release Capsules” to be at least half as large as the letters comprising the proprietary name such that the established name shall have a prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features in accordance with 21 CFR 201.10(g)(2).
3. Relocate the product strength statement away from the net quantity statement to appear immediately beneath the established name. From post marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
4. Add the statement “Swallow capsules whole. Do not crush or chew.” to the Dosage section on the side panel of the container label and the carton labeling

² Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Draft Guidance April 2013. Accessed March 4, 2015 online at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Durlaza that New Haven Pharmaceuticals Inc. submitted on December 10, 2014, and the United States Aspirin Monograph.

Table 2. Relevant Product Information for Durlaza and the Listed Drug		
Product Name	Durlaza	Aspirin
Initial Approval Date	N/A	OTC Monograph
Active Ingredient	Aspirin Extended-Release	Aspirin
Indication	<p>(b) (4)</p> <ul style="list-style-type: none"> Reduce the (b) (4) risk of death and (b) (4) stroke in patients who have had ischemic stroke or transient (b) (4) <p>(b) (4)</p> <ul style="list-style-type: none"> Reduce the (b) (4) risk of death and (b) (4) MI in patients with a (b) (4) MI or unstable angina pectoris <p>(b) (4)</p> <p>with chronic stable angina (b) (4)</p> <p>(b) (4)</p>	<p><u>Vascular Indications</u></p> <ul style="list-style-type: none"> Reduce 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 Reduce the risk of vascular mortality in patients with a suspected acute MI, <p>Reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris</p> <ul style="list-style-type: none"> Reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris <p><u>Revascularization Procedures</u></p> <ul style="list-style-type: none"> For patients who have undergone revascularization procedures (i.e., coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or carotid endarterectomy) when there is a preexisting condition for which acetylsalicylic acid (ASA) is already indicated. <p><u>Rheumatologic Disease Indications</u></p> <ul style="list-style-type: none"> For the relief of the signs and symptoms of rheumatoid arthritis,

		juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with systemic lupus erythematosus
Route of Administration	Oral	Oral
Dosage Form	Extended Release Capsules	Tablets
Strength	162.5 mg	N/A
Dose and Frequency	One capsule daily	<p>Anti-inflammatory and analgesic dosages should be individualized.</p> <p><i>Ischemic Stroke and TIA:</i> 50 – 325 mg once a day. Continue therapy indefinitely.</p> <p><i>Suspected Acute MI:</i> The initial dose of 160 – 162.5 mg is administered as soon as an MI is suspected. The maintenance dose of 160 –162.5 mg a day is continued for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.</p> <p><i>Prevention of Recurrent MI:</i> 75–325 mg once a day. Continue therapy indefinitely.</p> <p><i>Unstable Angina Pectoris:</i> 75–325 mg once a day. Continue therapy indefinitely.</p> <p><i>Chronic Stable Angina Pectoris:</i> 75–325 mg once a day. Continue therapy indefinitely.</p> <p><i>CABG:</i> 325 mg daily starting 6 hours post procedure. Continue</p>

	<p>therapy for 1 year post procedure.</p> <p><i>PTCA:</i> The initial dose of 325 mg should be given 2 hours pre-surgery. Maintenance dose is 160–325 mg daily. Continue therapy indefinitely.</p> <p><i>Carotid Endarterectomy:</i> Doses of 80 mg once daily to 650 mg twice daily, started presurgery, are recommended. Continue therapy indefinitely.</p> <p><i>Rheumatoid Arthritis:</i> The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 µg/mL. At high doses (<i>i.e.</i>, plasma levels of greater than 200 µg/mL), the incidence of toxicity increases.</p> <p><i>Juvenile Rheumatoid Arthritis:</i> Initial dose is 90–130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 µg/mL. At high doses (<i>i.e.</i>, plasma levels of greater than 200 µg/mL), the incidence of toxicity increases.</p> <p><i>Spondyloarthropathies:</i> Up to 4 g per day in divided doses.</p> <p><i>Osteoarthritis:</i> Up to 3 g per day in divided doses.</p> <p><i>Arthritis and Pleurisy of SLE:</i> The initial dose is 3 g a day in divided</p>
--	--

		doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 µg/mL. At high doses (<i>i.e.</i> , plasma levels of greater than 200 µg/mL), the incidence of toxicity increases.
How Supplied	90-count trade bottle and 30-count professional sample bottle	N/A
Storage	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).	N/A
Container Closure	30 mL and 100 mL HDPE bottles <div style="background-color: #cccccc; height: 1em; width: 100%;"></div> <small>(b) (4)</small>	N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Durlaza labels and labeling submitted by New Haven Pharmaceuticals Inc. on December 10, 2014, February 16, 2015, February 23, 2015, and February 24, 2015.

- Professional Sample Container Label submitted February 16, 2015
- Professional Sample Carton Labeling submitted February 24, 2015
- Container Label submitted February 16, 2015
- Carton Labeling submitted February 16, 2015
- Prescribing Information (no image) submitted February 23, 2015

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

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
03/16/2015

CHI-MING TU
03/16/2015

MEMORANDUM

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

DATE: February 05, 2015

TO: Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products
(DCRP)
Office of New Drugs

FROM: Srinivas Rao Chennamaneni, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

THROUGH: Charles R. Bonapace, Pharm.D.
Director (Acting)
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

SUBJECT: Acknowledgement of inspection request at (b) (4)
(b) (4)
and
Recommendation to accept data without on-site
inspection of (b) (4)

RE: NDA 200671
DRUG: DURLAZA (Controlled Release Aspirin) Capsules
SPONSOR: New Haven Pharmaceuticals

This memo acknowledges receipt of your request for inspections of the following bioequivalence (BE) study:

Study: NHP-ASP-01
Study Title: "A phase 1, open-label, four-way, randomized, crossover, single-dose, dose-response study comparing the pharmacodynamics and pharmacokinetics of NHP-554C capsules to immediate release aspirin capsules in healthy volunteers"

Analytical Site:

(b) (6)
(b) (6)

OSIS will conduct the inspection at (b) (6) (b) (6) as requested and will provide the review memo upon completion. OSIS requests that DCRP not reveal information regarding the inspection to the applicant or to the study site prior to the start of the inspection. The site will receive this information during the inspection opening meeting.

Clinical Site:

(b) (4)

The Office of Study Integrity and Surveillance (OSIS) recommends accepting the platelet aggregation data from Study NHP-ASP-01 without an on-site inspection of (b) (4). This memo provides the rationale for this recommendation and why OSIS is declining to inspect (b) (4).

OSIS inspected (b) (4) in (b) (4) twice in the last two years, covering two applications. The following is a list of applications with studies audited during those inspections, the study dates, the inspection dates, and the final inspectional classifications.

Application	Facility Type	Study Dates	Inspection Dates	Final Class
NON-RESPONSIVE				

Each inspection included a thorough review of all records associated with the studies and correspondence with the sponsors, records of subject sample receipt and storage, notebooks and electronic records, standard operating procedures (SOPs), as well as examination of facilities, and interviews and discussions with the firm's management and staff. No significant observations were identified during these inspections.

For the current study, NHP-ASP-01, the sponsor (New Haven Pharmaceuticals) examined three pharmacodynamic markers [Serum Thromboxane B2 (TxB2), urine 11-dehydro-TxB2, and Platelet aggregation] to determine efficacy of the DURLAZA Capsules. The platelet aggregation assay, which was conducted at (b) (4)

(b) (4) was carried out using a simple and rather semi-quantitative turbidimetric method. The platelet activity is dependent on TxB2 production and serum TxB2 data will be audited at (b) (6)

Conclusion:

Based on the satisfactory inspections in recent years, the final inspection classifications, the significance of the assay results for the current application, and the platelet aggregation assay methodology, this reviewer recommends accepting the platelet aggregation data from Study NHP-ASP-01 without an on-site inspection at (b) (4).

Srinivas Rao Chennamaneni, Ph.D.
DNDBE, OSIS, OTS

DARRTS cc:

OTS/OSIS/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Cho/
Chennamaneni/Dejernett/Nkah/Fenty-Stewart/Johnson
CDER/OND/ODEI/DCRP/Stockbridge/Blaus

Email cc:

ORA MIN BIMO mailbox

Draft: SRC 02/03/2015

Edit: JC 02/03/2015; CRB 02/04/2015

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence and Good
Laboratory Practice Compliance/INSPECTIONS/BE Program
/Analytical Sites/(b) (4) and
/Clinical Sites/(b) (4)

File: BE6793 (NDA 200671)

FACTS: (b) (4)

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/s/

SRINIVAS RAO N CHENNAMANENI
02/05/2015

CHARLES R BONAPACE
02/05/2015

OSI Consult Request for Biopharmaceutical Inspections

Date	10 December 2014
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sharon Turner-Rinehardt, RAC Project Manager Officer Office of Scientific Investigations sharon.turner-rinehardt@fda.hhs.gov
Consulting Office/Division	CDER/OND/ODEI/DCRP
Project Manager	Alison Blaus
Application Type	PEPFAR? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
	<input checked="" type="checkbox"/> NDA <input type="checkbox"/> BLA <input type="checkbox"/> ANDA
Application Number	200671
Drug Product	DURLAZA (controlled release aspirin) Capsules
Sponsor Name	New Haven Pharmaceuticals
Sponsor Address	965 West Main Street Branford, CT 06405
US Agent (if applicable)	Larry Dillaha, M.D. (Phone: 615-767-0074)
US Agent Address	965 West Main Street Branford, CT 06405
Electronic Submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PDUFA Due Date	5 July 2015
Action Goal Date	5 July 2015
OSI Review Requested By	5 May 2015

Inspection Request Detail (All fields should be fill out completely)			
Study #1			
Study Number	NHP-ASP-01		
Study Title	A phase 1, open-label, four-way, randomized, crossover, single-dose, dose-response study comparing the pharmacodynamics and pharmacokinetics of NHP-554C capsules to immediate release aspirin capsules in healthy volunteers		
Study Type	<input type="checkbox"/> In vivo BE	<input type="checkbox"/> In vitro BE	<input type="checkbox"/> Permeability <input checked="" type="checkbox"/> Others: Pivotal PK/PD study
<input checked="" type="checkbox"/> Inspection Request - Analytical Site			
Facility #1 Name:	(b) (4)		
Address:	(b) (4)		
(Tel)	(b) (4)		
Principal Analytical Investigator:	(b) (4), Ph.D., MBA		
Check one:	<input checked="" type="checkbox"/> Routine inspection <input type="checkbox"/> For cause		

Assays to be inspected

PD: Serum thromboxane B2

Laboratory identifier: (b) (4)

Author: (b) (4) Ph.D.

PD: Urine-11-dehydrothromboxane

Laboratory identifier: (b) (4)

Author: (b) (4), Ph.D.

PK: Acetylsalicylic acid and salicylic acid

Laboratory identifier: (b) (4)

Author: (b) (4), M.S.

Facility #2 Name: (b) (4)

Address: (b) (4)

Principal Analytical Investigator: Not available

Check one: Routine inspection
 For cause

Assays to be inspected

Platelet aggregation assay using arachidonic acid and collagen as agonists

Study Report: 5.3.4.1

Validation Report: 5.3.4.1

Bioanalytical Report: 5.3.4.1

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

Clinical pharmacology contact for this inspection request:

Sudharshan Hariharan, Ph.D.
10903 New Hampshire Avenue,
Bldg 51, Rm 2166
Silver Spring, MD 20993
Ph: 301-796-5683
E-mail: Sudharshan.Hariharan@fda.hhs.gov

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/s/

ALISON L BLAUS
12/10/2014

SUDHARSHAN HARIHARAN
12/10/2014

RAJANIKANTH MADABUSHI
12/10/2014

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 # 200671 BLA# n/a	NDA Supplement #:S- n/a BLA Supplement # n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: DURLAZA Established/Proper Name: controlled release ASA Dosage Form: capsules Strengths: 162.5 mg		
Applicant: New Haven Pharmaceuticals Agent for Applicant (if applicable): n/a		
Date of Application: 5 September 2014 Date of Receipt: 5 September 2014 Date clock started after UN: n/a		
PDUFA Goal Date: 5 July 2015	Action Goal Date (if different): n/a	
Filing Date: 4 November 2014	Date of Filing Meeting: 27 October 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Secondary Prevention of Cardiovascular Events		
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:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare 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 <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <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 (if OTC product):				
List referenced IND Number(s): 116348				
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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Goals were not included in DARRTS. Eric ticket has been opened.
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

<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 type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" 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><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></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><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></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><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></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><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></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><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: FIVE <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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 the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <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.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		3454 Included

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
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, <u>both</u> 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Electronic submission
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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
PREA 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Notified PeRC and scheduled for the 12Nov14 meeting
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BPCA (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>	<input type="checkbox"/>	<input type="checkbox"/>		n/a
Proprietary Name	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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Requested from the applicant and submitted 25Sep14
REMS	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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult dated 22Sep14
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult dated 22Sep14
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult dated 22Sep14
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>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<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?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Clinical Pharmacology Consult needed for BE Study.
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): n/a	<input type="checkbox"/>	<input type="checkbox"/>		n/a
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Preliminary comments sent and meeting cancelled by sponsor.	<input type="checkbox"/>	<input type="checkbox"/>		Preliminary comments dated 30 August 2013
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): n/a	<input type="checkbox"/>	<input type="checkbox"/>		n/a
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 27 October 2014

NDA #: 200671

PROPRIETARY NAME: Durlaza

ESTABLISHED/PROPER NAME: controlled release aspirin

DOSAGE FORM/STRENGTH: 162.5 mg capsules

APPLICANT: New Haven Pharmaceuticals (NHP)

PROPOSED INDICATION: Secondary prevention of acute cardiovascular events

BACKGROUND: Durlaza is a controlled release aspirin product (b) (4) (b) (4) being developed in the USA by NHP. On 10 December 2009 and 23 November 2010 (minutes dated 28 December 2009 and 2 December 2010 respectively) the sponsor attended a pre-NDA meeting (under NDA 200671) where a number of agreements were made, among them the sponsor's acceptance of the Agency's requirement that they conduct the dose-PD response (thromboxane B2 and platelet aggregation inhibition) study entitled, "A Phase 1 Open-label, Four-way, Randomized, Crossover, Single-Dose, Dose-Response Study Comparing the Pharmacodynamic of Micropump® Aspirin Capsules to Immediate-Release Aspirin Capsules in Healthy Volunteers". They also agreed to provide long-term stability testing covering a minimum of 12 months duration on at least three primary batches. In lieu of a third pre-NDA meeting, preliminary comments were sent to the sponsor and those are dated 30 August 2013.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Ed Fromm	Y
Cross-Discipline Team Leader (CDTL)	Raj Madabushi		Y
Clinical	Reviewer:	Fred Senatore	Y
	TL:	Tom Marciniak	N
Social Scientist Review (for OTC products)	Reviewer:	n/a	n/a

	TL:	n/a	n/a
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Pharmacology	Reviewer:	Sudharshan Hariharan	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Steve Bai	N
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Belay Tesfamariam	Y
	TL:	Al DeFelice	N
Statistics (carcinogenicity)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Product Quality (CMC)	Reviewer:	Shastri Bhamidipati (DP) Lyudmila Soldatova (DS) Sandra Suarez (Biopharm)	N Y Y
	TL:	Kasturi Srinivasachar Angelica Dorantes	N N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
CMC Labeling Review	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DMEPA (proprietary name)	Reviewer:	Janine Stewart	Y

	TL:	Chi-Ming Tu	N
OSE/DRISK (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Bioresearch Monitoring (OSI)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers	Zarna Patel (OPDP)		N
Other attendees	Norman Stockbridge (Division Director), Stephen Grant (Deputy Division Director and Division Sign-off), Anne Tobenkin (safety evaluator), and Cherye Milburn (OSE RPM)		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>BE Studies were conducted. Applicant needs to resubmit the 356h and reference the complete aspirin OTC monograph and not just the professional labeling portion. Request to be included in the 74-day letter.</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

If no , explain:	
<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 <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments: No issues for the 74-day Letter	
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: 505(b)(2) application and no pivotal clinical trials were conducted.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: See Reason.</p> <p>If no, for an NME NDA or original BLA , include the reason. For example:</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 checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: 505(b)(2) application and no issues that need the input from the AC members.
<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
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE

Comments:	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<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
Comments: No issues for the 74-day Letter.	
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<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
Comments:	
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<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
Comments: No issues for the 74-day Letter.	
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<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
Comments:	
PRODUCT QUALITY (CMC)	<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
Comments: None.	
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
If no , was a complete EA submitted?	<input type="checkbox"/> YES <input type="checkbox"/> NO
If EA submitted , consulted to EA officer (OPS)?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

<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:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<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:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></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><u>CMC Labeling Review</u></p> <p>Comments: n/a</p>	<input type="checkbox"/> Review issues for 74-day letter
<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? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	n/a

<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? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Stephen Grant, M.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 2 February 2015</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments: n/a</p>	
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): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input 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"/>	If priority review: <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"/>	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: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input checked="" type="checkbox"/>	Other – Clinical Pharmacology Inspection Consult to be finalized and the goals need to be included in DARRTS (ERIC ticket opened).

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

/s/

ALISON L BLAUS
11/14/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 200671

Application Type: New NDA

Name of Drug/Dosage Form: DURLAZA (controlled release aspirin) Capsules

Applicant: New Haven Pharmaceuticals

Receipt Date: 5 September 2014

Goal Date: 5 July 2014

1. Regulatory History and Applicant's Main Proposals

Please see the RPM Filing Overview

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (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. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Please remove the confidentiality warning in the footer.
2. For clarity, please define all abbreviations and acronyms upon its first appearance in the Full
3. Prescribing Information (FPI).
4. The beginning of the ADVERSE REACTIONS (AR) section (before the subsection 6.1) should identify the most clinically significant AR and direct practitioners to more detailed information about those reactions, if any. For example, the section should first identify and cross-reference all serious and otherwise potentially important AR described in greater detail in other labeling sections, especially WARNINGS AND PRECAUTIONS.
5. Per 21 CFR 201.57, please amend Section 8.4, **Pediatric Use**, to read, "Safety and effectiveness have not been established in pediatric patients."
6. Please delete Section 9, Drug Abuse and Dependence. This section should only be included when there is information to convey.
7. Upon review of the Medication Guide, we have the following comments:

Selected Requirements of Prescribing Information

- a. Please note that the US Package Insert and the Medication Guide will be separate document if approved. As of right now, your manufacturing and marketing information only appears in the Medication Guide.
- b. In the Medication Guide, please un-bold the following statement, “This Medication Guide has been approved by the U.S. Food and Drug Administration.”.
- c. Overall word simplification is needed. Technical terms should be removed if possible and replaced. For example, “healthcare provider” should be updated to “doctor”.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by **10 December 2014**. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

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

HIGHLIGHTS GENERAL FORMAT

- 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:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *The highlights is more than one page. Please limit the information in the highlights to a half-page*

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *There is no horizontal line between the TOC and FPI. Please add a line.*

- 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:

- YES** 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.

Comment:

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

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• 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

- YES** 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:

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**.

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

Selected Requirements of Prescribing Information

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: Please include pharmacologic class. The first sentence should read, “DURLAZA is a Nonsteroidal Anti-inflammatory Drug indicated ^(b)₍₄₎”.

Dosage Forms and Strengths in Highlights

- NO** 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: Please add bullets for each population to help differentiate the groups.

Selected Requirements of Prescribing Information

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

- NO** 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: Please include your company name and the contact information.

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: Please change [REDACTED] ^{(b) (4)} TO “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”.

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:
- YES** 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:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- 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

- YES** 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:

- 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: In your cross-reference, please include the referenced subsection when appropriate as well (e.g., [see Warnings and Precautions (5.2)]).

- 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:

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

- NO** 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: Please include a subsection under Section 6 entitled, “Clinical Trials Experience”. Per 21 CFR 201.57(c)(7), the first statement in this subsection should be, “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.”.

- N/A** 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:

“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

Selected Requirements of Prescribing Information

not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 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: *Please include Section 17 in the FPI and include the important information that the physician should communicate to the patient.*

- 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: *Please make the Medication Guide a standalone page (either within the same file or a separate file).*

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]

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

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/

ALISON L BLAUS
11/14/2014